Evidence Report:

Chronic Kidney Disease and Commercial Motor Vehicle Driver Safety

Presented to:

Federal Motor Carrier Safety Administration

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Prepared for

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Evidence reports are sent to the Federal Motor Carrier Safety Administration's (FMCSA) Medical Review Board (MRB) and Medical Expert Panels (MEP). The MRB and MEP make recommendations on medical topics of concern to FMCSA.

FMCSA will consider all MRB and MEP recommendations, however, all proposed changes to current standards and guidance (guidelines) will be subject to public-notice-and-comment and relevant rulemaking processes.

Policy Statement

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Executive Summary

Purpose of Evidence Report

Commercial driving is a hazardous occupation. Of all occupations in the United States, workers in the trucking industry experience the third highest fatality rate, accounting for 12 percent of all worker deaths. About two thirds of fatally injured truck workers were involved in highway crashes. According to statistics from the U.S. Department of Transportation (DOT), there were 4,932 fatal crashes involving a large truck in 2005, for a total of 5,212 fatalities. In addition, there were 137,144 nonfatal crashes; 59,405 of these were crashes that resulted in an injury to at least one individual (for a total of 89,681 injuries).

The purpose of this evidence report is to address several key questions posed by the Federal Motor Carrier Safety Administration (FMCSA). FMCSA developed each of these key questions so that the answers will provide information useful in updating its current medical examination guidelines. The four key questions addressed in this evidence report are:

Key Question 1: Are individuals with kidney disease at an increased risk for a motor vehicle crash?

Key Question 2: Are medications used to treat individuals with kidney disease associated with an increased risk of motor vehicle crash among pre-dialysis patients?

Key Question 3: Are dialysis and accompanying drug treatments associated with an increased risk of motor vehicle crash?

Key Question 4: Are kidney transplantation and accompanying drug treatments associated with an increased crash risk?

Identification of Evidence Bases

We identified separate evidence bases for each of the key questions this evidence report addresses using a process consisting of a comprehensive search of the literature, an examination of abstracts of identified studies to determine which articles would be retrieved, and selection of the actual articles to be included in each evidence base.

We searched seven electronic databases (Medline, PubMed (PreMEDLINE), EMBASE, PsycINFO, CINAHL, TRIS, and the Cochrane library) (through September 12, 2007). In addition, we examined the reference lists of all obtained articles with the aim of identifying relevant articles not identified by our electronic searches. Hand searches of the "gray literature"

were also performed. We admitted articles to an evidence base by formal retrieval and inclusion criteria determined *a priori*.

Grading the Strength of Evidence

Our assessment of the quality of the evidence took into account not only the quality of the individual studies that comprise the evidence base for each key question; but also the interplay between the quality, quantity, robustness, and consistency of the overall body of evidence.

Presentation of Findings

In presenting our findings, we typically make a clear distinction between qualitative and quantitative conclusions, and we assign a separate strength-of-conclusion rating to each conclusion format. The limited quantity of evidence in each evidence base and the differences in those studies precluded us from forming quantitative conclusions in this evidence report. The strength-and-stability-of-evidence ratings assigned to these different types of conclusions are defined in Table 1.

Table 1. Strength-and-Stability-of- Evidence Ratings for Qualitative and Quantitative Conclusions

Strength of Conclusion	*Interpretation*
Qualitative Conclusion	
Strong evidence	Evidence supporting the qualitative conclusion is convincing. It is highly unlikely that new evidence will lead to a change in this conclusion.
Moderate evidence	Evidence supporting the qualitative conclusion is somewhat convincing. There is a small chance that new evidence will overturn or strengthen our conclusion. ECRI Institute recommends regular monitoring of the relevant literature for moderate-strength conclusions.
Acceptable evidence	Although some evidence exists to support the qualitative conclusion, this evidence is tentative and perishable. There is a reasonable chance that new evidence will either overturn or strengthen our conclusions. ECRI Institute recommends frequent monitoring of the relevant literature.
Unacceptable	Although some evidence exists, the evidence is insufficient to warrant drawing an evidence-based conclusion. ECRI Institute recommends frequent monitoring of the relevant literature.
Quantitative Conclusion (Stability of Effect-size Estimate)	
High stability	The estimate of treatment effect in the conclusion is stable. It is highly unlikely that the magnitude of this estimate will change substantially as a result of the publication of new evidence.
Moderate stability	The estimate of treatment effect in the conclusion is somewhat stable. There is a small chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI Institute recommends regular monitoring of the relevant literature.
Low stability	The estimate of treatment effect included in the conclusion is likely to be unstable. There is a reasonable chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI Institute recommends frequent monitoring of the relevant literature.
No stability	Estimates of the treatment effect are too unstable to allow a quantitative conclusion to be drawn at this time. ECRI Institute recommends frequent monitoring of the relevant literature.

Findings

We summarize the findings of our analyses of the data pertaining to the four key questions addressed in this evidence report below.

Key Question 1: Are individuals with kidney disease at an increased risk for a motor vehicle crash?

Current direct evidence from crash studies does not demonstrate that individuals with kidney disease are at an increased risk for a crash. Indirect evidence, albeit weak, does suggest that it is plausible that individuals with kidney disease may be at increased risk for a motor vehicle crash (Strength of Conclusion: Acceptable).

Direct Evidence – Crash Studies*: Our searches identified two direct crash-risk studies with a total of 94 individuals with kidney disease. It is unclear how similar the drivers in these studies are to commercial motor vehicle (CMV) drivers because few characteristics of the drivers are reported; however, it does not appear that CMV drivers are represented. Driving exposure was not adequately controlled for in either study. For this and additional reasons, these studies were both rated low in quality. One retrospective cohort study reported on the crash rate among individuals with chronic kidney disease compared with the rate among community controls. The other study, a case-control study, reported on the proportion of individuals with kidney disease among a cohort of individuals who crashed compared with the proportion of drivers with kidney disease among a cohort of individuals who did not crash. Neither of these studies provided evidence in support of the contention that individuals with kidney disease are at an increased risk for a motor vehicle crash. On the contrary, both studies actually found that individuals with kidney disease appear to be at a reduced risk for a crash.*

Indirect Evidence—Studies of Neurocognitive Function*: Eight studies with a total of 489 patients assessed neurocognitive impairment of people with kidney disease. Overall the evidence base was of low quality. Differences among the studies included varied types of study designs, controls selected, and outcomes reported. The eight studies reported outcomes on a total of 18 neurocognitive measurements in four domains: general neurocognition, attention and concentration, visuospatial skill, and executive function. There was no consensus among studies to definitively conclude that people with kidney disease have neurocognitive impairment. However, there is a sufficient quantity of evidence that on multiple outcome measures with different groups of patients tested in different study designs, kidney disease is associated with impaired neurocognition. Therefore, the possibility that people with kidney disease experience neurocognitive impairment cannot be dismissed.*

Indirect Evidence—Studies of Sleep-Related Outcomes*: Only one study with 46 patients addressed this outcome. The study was of low quality. Generalizability to the CMV driver*

population is uncertain. The authors found that the prevalence of severe sleep-disordered breathing among enrolled patients with kidney disease was four times that of the controls from a general population, but no significant difference was found on other outcomes important to safe operation of a motor vehicle, including daytime sleepiness. However, previous systematic reviews have associated sleep-disordered breathing with an actual increase in motor vehicle crash. Therefore, this evidence suggests that people with kidney disease are at a greater risk of motor vehicle crash than people without.

Key Question 2: Are medications used to treat individuals with kidney disease associated with an increased risk of motor vehicle crash among pre-dialysis patients?

No conclusions regarding the effect of medications on crash risk in pre-dialysis kidney disease patients can be drawn at the present time.

Our searches, including both electronic and hand searches, did not identify any studies that assessed the association of medications in pre-dialysis kidney disease patients on direct or indirect crash risk.

Key Question 3: Are dialysis and accompanying drug treatments associated with an increased risk of motor vehicle crash?

There is currently no direct evidence of an association between dialysis and the risk of a motor vehicle crash. However, indirect evidence indicates that it is plausible that drivers with end-stage renal disease (ESRD) treated with dialysis and related medications may be at an increased risk of motor vehicle crash (Strength of Conclusion: Acceptable).

***Direct Evidence – Crash Studies**: No studies were identified by our searches.*

***Indirect Evidence – Studies Neurocognitive Function**: We identified 13 studies with 980 patients with unclear generalizability to CMV drivers. Overall, this evidence base was of low quality. The included studies used a variety of study designs and different control populations, limiting their comparability and compatibility for statistical analysis. Furthermore, studies infrequently reported the same outcomes. For analysis, we subdivided the studies by comparisons performed. No clear trend emerged from these 13 studies to conclude definitively that patients treated with dialysis do or do not have neurocognitive impairment compared with controls. However, a substantial number of test results suggest that patients treated with dialysis do have neurocognitive impairment in domains associated with an increased risk of motor vehicle crash. Findings also suggest that ESRD patients on hemodialysis may be more impaired than patients not on dialysis, and that patients on hemodialysis may be more impaired the day before dialysis than the day after.*

Indirect Evidence – Studies of Sleep-Related Outcomes*: Three studies with a total of 70 patients were identified for this evidence base. Each addressed different outcomes and therefore had to be considered in isolation. The findings of two studies point to an association between sleep disorders and kidney disease, indirectly suggesting an increased risk of motor vehicle crash among dialysis patients. The findings of one of those studies also suggest that overnight (nocturnal) dialysis may alleviate sleep apnea. The findings of the third study suggest that different dialysis buffers may alleviate symptoms.*

Key Question 4: Are kidney transplantation and accompanying drug treatments associated with an increased risk of motor vehicle crash?

Currently, there is no direct evidence associating kidney transplantation and motor vehicle crash risk. However, indirect evidence suggests the possibility that kidney transplant recipients may be at a lower risk for motor vehicle crash than individuals with ESRD treated with dialysis (Strength of Conclusion: Acceptable).

Direct Evidence – Crash Studies*: Our searches identified no studies.*

Indirect Evidence – Neurocognitive Function*: Two low- quality studies that enrolled a total of 43 kidney transplant recipients met the inclusion criteria for this key question and reported on neurocognitive function. One study observed significant improvements in neurocognitive function among kidney transplant recipients across several domains. The second study observed some small improvements in neurocognitive function, but these improvements were not statistically significant. Given the small size of this study, the lack of a statistically significant finding is not surprising and this finding may be an example of a type-II statistical error. Neither of these studies specifically enrolled individuals from a population of CMV drivers. Consequently, the generalizability of the findings of these two studies to CMV drivers is unclear.*

Indirect Evidence - Sleep-Related Outcomes*: One low-quality study that enrolled 841 kidney transplant recipients met the inclusion criteria for this key question and reported on a sleep-related outcome. The generalizability of this study to CMV drivers is unclear. The study findings suggest that a substantial portion of kidney transplant recipients may be at risk for sleep apnea, and therefore at an increased risk of motor vehicle crash. However, a smaller proportion of kidney transplant recipients were at risk for sleep apnea compared with similar individuals on dialysis, suggesting that the risk of motor vehicle crash among transplant recipient may be lower among transplant recipients than dialysis patients.*

Preface

Organization of Report

This evidence report contains three major sections: (1) *Background*, (2) *Methods*, and (3) *Synthesis of Results.* These major sections are supplemented by extensive appendices.

In the *Background* section, we provide information about kidney disease, including its epidemiology, diagnosis, treatment, and potential impact on driver safety. Also, the *Background* section contains information about kidney disease-related standards and guidelines for CMV operators in the United States and several other countries. In addition, we provide information pertaining to commercial pilots, merchant mariners, and railcar operators. In the *Methods* section, we detail how we identified and analyzed information for this report. The section covers the key questions addressed, details of literature searches, criteria for including studies in our analyses, evaluation of study quality, assessment of the strength of the evidence base for each question, and methods for abstracting and synthesizing clinical study results. The *Synthesis of Results* section is organized by key question. For each question, we report on the quality and quantity of the studies that provided relevant evidence. We then summarize available data extracted from included studies either qualitatively or, when data permit, qualitatively and quantitatively (using meta-analysis). Each part in the *Synthesis of Results* section closes with conclusions based on our assessment of the available evidence.

Scope of Report

The purpose of this evidence report is to address several key questions posed by FMCSA. Each key question was carefully formulated by FMCSA so that its answer will provide information necessary for updating its report, "Conference on Renal Failure and Commercial Drivers." The key questions addressed in this evidence report are as follows:

Key Question 1: *Are individuals with kidney disease at an increased risk for a motor vehicle crash*?

Key Question 2: *Are medications used to treat individuals with kidney disease associated with an increased risk of motor vehicle crash among pre-dialysis patients*?

Key Question 3: *Are dialysis and accompanying drug treatments associated with an increased risk of motor vehicle crash?*

Key Question 4: *Are kidney transplantation and accompanying drug treatments associated with an increased risk of motor vehicle crash?*

Background

Kidney disease, its comorbidities, complications, and treatments, have a complex interrelationship that may increase the potential risk of a motor vehicle crash. ESRD can result in fluid, electrolyte, and mineral imbalances that can cause sudden incapacitation through seizure, shock, neurological complications, or cardiac disease. Symptoms associated with chronic kidney disease or its treatment, such as fatigue and drowsiness or cognitive impairment, may also increase risk of crash. The purpose of this section is to provide an overview of kidney disease, with special attention to the potential for its effect on the ability of an individual to safely operate a CMV.

Kidney disease

Healthy kidneys perform many vital functions, including:(15)

- Regulation of blood ionic composition
- Regulation of blood pH
- Regulation of blood volume
- Regulation of blood pressure
- Maintenance of blood osmomolarity
- Production of hormones, including those that stimulate the production of red blood cell formation
- Regulation of blood glucose levels
- Excretion of waste products from the blood

Kidney disease impairs the ability of kidneys to perform their usual functions. The effects of this impairment may go unnoticed in the early stages. Advanced kidney disease, especially ESRD, can cause toxic buildups of protein metabolic by-products and reduce red blood cell production.(15) The resulting fluid imbalance, buildup of toxins, and anemia produce many vague signs and symptoms, including fatigue, difficulty concentrating, decreased appetite, impaired sleep, muscle cramping (especially at night), swollen feet and ankles, fluid retention around the eyes, dry and itchy skin, and frequent urination.(16) Kidney disease is also associated with an increased risk of life-threatening complications such as cardiovascular disease.

Acute Renal Failure

In acute renal failure, renal function declines rapidly over hours or days. Acute renal failure is typically defined by a reduction in serum creatinine of ≥0.5 mg/deciliter (44 μmol per liter) from

baseline, a ≥50 percent reduction in creatinine clearance, or a decrease in renal function severe enough to warrant dialysis.(17) It can be caused by factors that reduce prerenal perfusion (e.g., poor fluid intake or heart failure), obstructed urinary outflow (e.g. prostatic hypertrophy or cancer, or retroperitoneal disorders), or cause failure within the kidney (e.g., ischemic or toxic injury to the tubules).(17) The majority of cases of acute renal failure are caused by ischemia and toxin exposure.(17) Patients who have acute renal failure will not necessarily develop chronic renal failure. One retrospective study of 26 consecutive patients with acute renal failure who required dialysis for at least four weeks found that 88 percent successfully discontinued dialysis treatment.(18)

Chronic Kidney disease

Chronic kidney disease is typically diagnosed when the glomerular filtration rate of the kidneys falls to 60 mL per minute per 1.73 m^2 or less for three months or longer. Chronic kidney disease is usually irreversible and progressive. The most common cause of chronic ESRD in the United States is diabetes, followed by hypertension. Additional causes (in decreasing order of prevalence) include primary or secondary glomerulonephritis, interstitial nephritis, cystic, congenital or heritable nephritis, and neoplasms and tumors.

The Classification of Kidney disease

Understanding the causes and extent of kidney disease is critical in determining optimal treatment options and the type and potential for complications that might occur. In the classification schedule used by the National Kidney Foundation, the stage of kidney disease is determined by glomerular filtration rate (GFR), which is defined as the rate at which renal filtrate forms in the renal corpuscle per minute.(19) Normal GFR rates are varied across the U.S. population: values are typically lower in women than in men; in older people than in younger people; in Hispanics, Asians, and Caucasians than in African-Americans; and in vegetarians than in non-vegetarians.(19)

GFR cannot be directly measured; it must be calculated based on serum creatinine values, body surface area, and demographic characteristics. There are two equations commonly used to calculate GFR. The Cockcroft-Gault formula (Equation 1) was developed in 1973 and may overestimate GFR.(19) Although the original Cockcroft-Gault formula did not account for body surface area, the version of the formula shown in Equation 1, from the National Kidney Foundation, does take this factor into account. The MDRD Equation (named for the Modification of Diet in Kidney disease Study Group, which developed it) (Equation 2) was published in 1999, and takes body surface area and African-American ethnicity into account. It is considered more accurate than the Cockcroft-Gault equation.(19) In both formulae, serum creatinine in mg/dL is denoted S_c

Equation 1. The Cockcroft-Gault Equation

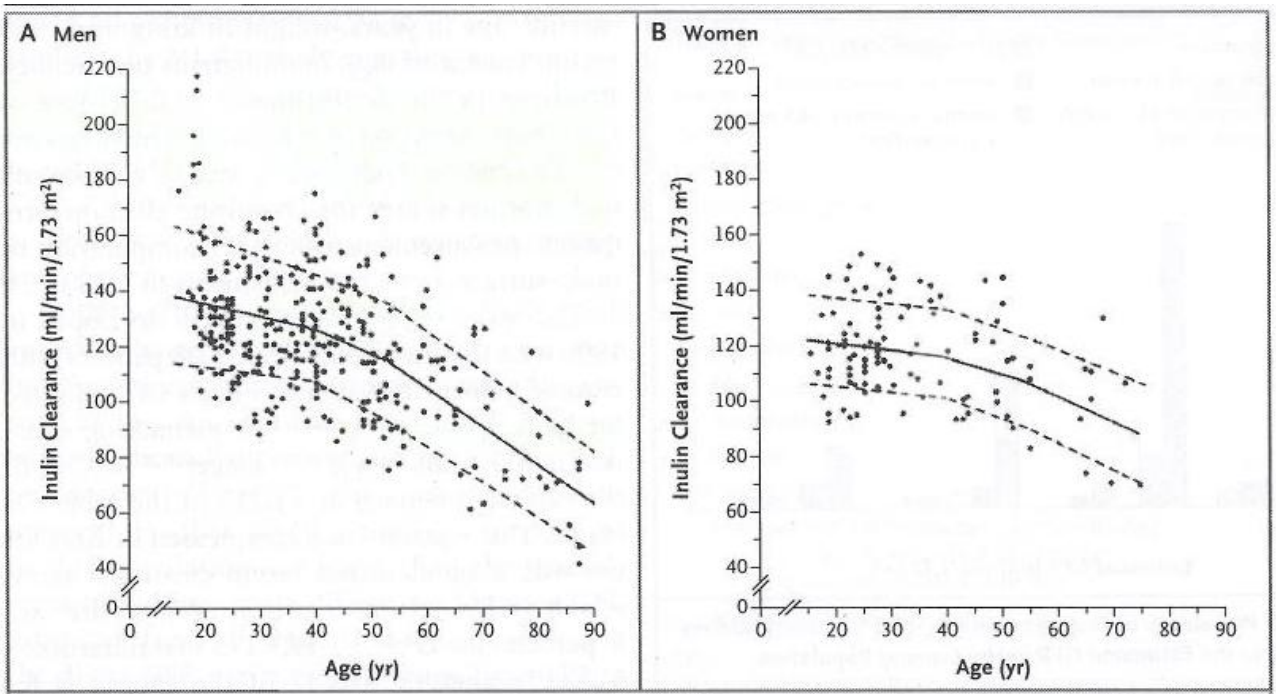
$$C_{cr} = \frac{(140 - age) \times weight}{72 \times S_{Cr}} \times (0.85\ if\ subject\ is\ female) \times (0.20247 \times height(m)^{0.725}) \times weight(kg)$$

Equation 2. MDRD Study Equation

$$GFR = 186 \times (S_{cr})^{-1.154} \times age^{-0.203} \times (0.742\ if\ subject\ is\ female) \times (1.1212\ if\ subject\ is\ black)$$

Normal GFR values are approximately 130 mL/minute/1.73 m^2 in young men, and 120 mL/minute/1.73m^2 in young women.(19) It is normal for GFR to decline with age and for values to be lower in women than in men. Normal GFR rates by age and gender are shown in Figure 1.

Figure 1. Normal GFR Values as a Function of Age



From Stevens et al. 2006(19). Solid lines represent the means, and dashed lines represent one standard deviation from the mean

GFR values of 60 mL/minute/1.73m^2 or lower are considered indicative of kidney disease. According to the National Kidney Foundation's, diagnosis scale, there are five stages of chronic kidney disease; the fifth stage—kidney failure or ESRD—is the most advanced stage. Table 2 describes the stages of chronic kidney disease.

Table 2. Stages of Chronic Kidney disease

Stage	Description	Glomerular Filtration Rate (GFR)	Prevalence in US Population
Increased Risk	Individual has a risk factor for kidney disease (e.g. diabetes, high blood pressure, family history, older age, ethnic group)	≥90 mL/min/1.73 m^2	(Not reported)
1	Renal damage (protein in urine) and normal GFR	≥90 mL/min/1.73 m^2	5.9 million (3.3%)
2	Renal damage and mild decrease in GFR	60-89 mL/min/1.73 m^2	5.3 million (3.0%)
3	Moderate decease in GFR	30-59 mL/min/1.73 m^2	7.6 million (4.3%)
4	Severe decrease in GFR	15-29 mL/min/1.73 m^2	400,000 (0.2%)
5	Renal Failure (also known as ESRD)	≤15 mL/min/1.73 m^2	300,000 (0.2%)

From the National Kidney Foundation Disease Outcomes Quality Initiative (NKF-K/DOQI) Clinical Practice Guidelines for Chronic Kidney Disease

Individuals with stages 1 through 3 of kidney disease usually do not experience any signs or symptoms of the disorder. The symptoms of kidney disease typically appear at stages 4 or 5, when changes in water or electrolyte balance, or endocrine or metabolic problems become clinically evident. Individuals with stage 5 renal failure may also develop uremic signs and symptoms, which are believed to be caused by the accumulation of toxins.(20) Signs and symptoms of uremia include: pericarditis, encephalopathy, peripheral neuropathy, restless legs syndrome, anorexia, nausea, vomiting, diarrhea, dry skin, pruritus, ecchymosis, fatigue, increased somnolence, failure to thrive, malnutrition, erectile dysfunction, decreased libido, amenorrhea, and platelet dysfunction.(20)

Risk Factors for Kidney disease

Risk factors that may be associated with the development of kidney disease include:(21-27)

- Diabetes, especially when albuminuria is present
- Hypertension
- Overweight and Obesity
- Hyperlipidemia
- Advanced Age
- HIV
- Heavy use of over-the-counter analgesics, including acetaminophen, aspirin, and non-steroidal anti-inflammatory drugs (NSAIDs)
- Family history (Thought to be from multiple genetic and environmental factors)

- Ethnicity (Native Americans, Hispanics, and African Americans are at greater risk than Caucasians)

The pathophysiology of diabetes and hypertension can precipitate the development of chronic kidney disease, and in turn, chronic kidney disease can contribute to hypertension. Among patients with chronic kidney diseases, 70 to 71 percent of patients aged 50 and older with private health insurance and at least 90 percent of Medicare patients are diagnosed with diabetes, hypertension, or both.(28) Worldwide, diabetic nephropathy is responsible for about a third of all ESRD cases.(26) Diabetes accounts for 30 to 40 percent of all cases of ESRD and is the leading cause of chronic kidney disease in the United States(29)

Being overweight or obese has become recognized as "the number one preventable risk factor for chronic kidney disease," presumably because of the relationship between excess weight, hypertension and type II diabetes.(30) However, studies have found that being overweight is an independent risk factor for the development of chronic kidney disease.(22,30,31)

Some risk factors are associated not only with the onset of kidney disease, but also with the hastened progression of kidney disease to ESRD. These factors include modifiable risk factors, namely smoking, hypertension, hyperglycemia, hyperlipidemia, and obesity.(31-33) In overweight individuals, weight reduction has been associated with improved glomerular hemodynamics and reduced albumin excretion.(34) Treating dyslipidemia with statins has also been shown to slow the progression of kidney disease; however, it remains unclear whether this is caused by reduced serum cholesterol or the medication's pleiotropic effects, such as improved endothelial function, enhanced stability of atherosclerotic plaques, decreased oxidative stress and inflammation, and inhibited thrombogenic response.(33) These pleiotropic effects are also thought to prevent coronary heart disease.(35)

Pathophysiology of Kidney disease

As stated previously, kidney disease is the impaired ability of kidneys to perform their usual functions, including regulation of electrolytes, fluids, acid-base balance, and stimulation of red blood cell production. The three main physiological functions of nephrons, the functional unit of the kidney, are glomerular filtration, tubular resorption, and tubular section. In glomerular filtration, water and most solutes from blood plasma move across glomerular capillary walls into the glomerular capsule. When this process is impaired, GFR decreases. Decreased rates of glomerular filtration are an indicator of kidney disease, and calculation of GFR is the accepted and common way to assess renal function. If GFR is reduced, tubular filtration (resorption of filtered water and solutes) and tubular secretion rates (removal of wastes from the blood) are also reduced. Without proper filtration, reabsorption and secretion, blood volume and composition may not be adequately maintained.

Numerous factors can cause the damage that affects the optimal performance of the nephrons. Disruptions in renal autoregulation, neural regulation, and hormonal regulation can all decrease GFR.(15) Chronic hypertension can cause vascular wall changes that diminish renal blood flow, causing inappropriate changes in the arterioles that preserve single-nephron GFR.(36) Diabetes can decrease renal function in many ways, including increasing oxidative stress through the polyol pathway, modification of extracellular matrix and circulating proteins by gene transcription regulators through nonenzymatic glycosylation, and increased vasoconstriction as the sequelae of hyperglycemia.(36) Additional deleterious factors include the effects of congenital abnormalities, smoking, toxins, trauma, and infections.

Effects of Kidney disease

Kidney disease has many effects. Patients may not experience any of the common symptoms of kidney disease until renal function has declined by as much as 75 to 90 percent. Some of these symptoms (see Table 3) may be related to decreased renal function, the medications administered to treat it, or a combination of the two. They may also be associated with common comorbidities linked with, (and possibly caused by) kidney disease, such as anemia, cardiovascular disease, and hypertension.

Table 3. Common Symptoms of Kidney disease

Symptom	Weighted mean prevalence	Ranges Reported in Surveyed Literature
Fatigue/tiredness	71%	12% to 97%
Pruritis	55%	10% to 77%
Constipation	53%	8% to 57%
Anorexia	49%	25% to 61%
Pain	47%	8% to 57%
Anxiety	38%	12% to 52%
Dyspnea	35%	11% to 55%
Nausea	33%	15% to 48%
Restless legss	30%	8% to 52%
Depression	27%	5% to 58%

Produced from data in Murtagh et al. 2007(37)

Anemia

Chronic kidney disease causes anemia by preventing erythropoietin production, meaning sufficient hemoglobin for red blood cells cannot be produced. Symptoms of anemia include fatigue, cognitive impairment, and angina. An estimated 2 to 4 million of the 20 million people with chronic kidney disease in the United States have anemia.(38) Anemia may also be more common among people with diabetes. In one study it was more frequently observed in patients with stage III-IV chronic kidney disease and diabetes (62 percent) than in non-diabetic patients with chronic kidney disease and comparable GFR (52 percent).(39)

Anemia may be associated with cardiorenal anemia syndrome, which is typified by progressive anemia, chronic kidney disease, and congestive heart failure.(38) In a long-term longitudinal study (median follow-up 8.6 years), patients with diabetes, chronic kidney disease, and anemia had a hazard ratio of 1.64 (95 percent CI 1.03 to 2.61) for myocardial infarction or fatal coronary heart disease, 1.81 (95percent CI 0.99 to 3.29) for stroke, and 1.88 (95 percent CI 1.33 to 2.66) for all-cause mortality.(40) Some researchers have found that treatment of anemia may prevent chronic kidney disease progression and improve function.(38)

Anemia in drivers with chronic kidney disease is important to consider, as anemia has been associated with increased risk of at-fault motor vehicle crash in experimental studies. In one study of assignment of culpability among 7,750 consecutive drivers (including noncommercial drivers) with complete records who crashed and were admitted to a hospital for their injuries, drivers with anemia were 1.34 times more likely (95 percent CI 1.13 to 1.59) to be considered at fault for their crash than all drivers in the sample.(41)

Hypertension

Hypertension and chronic kidney disease are interrelated. Hypertension can lead to chronic kidney disease, and chronic kidney disease can exacerbate hypertension. The two conditions frequently appear together, even when signs of chronic kidney disease are mild. Mechanisms by which diseased kidneys contribute to hypertension include plasma volume expansion, sodium retention, sympathetic nervous system and renin-angiotensin-aldosterone axis hypertension, and accumulation of endogenous vasoactive substances.(42,43) Increasing levels of hypertension appear to contribute to the development of left ventricular hypertrophy, increasing cardiovascular disease risk.(43) Both hypertension and hypotension (a marker for cardiac failure) were associated with increased mortality rates in ESRD.(44)

The high prevalence of hypertension with chronic kidney disease(24) should be considered when assessing the probability of drivers with kidney disease to crash. An evidence report has found that drivers with hypertension are at an increased risk of crash compared with similar drivers with normal blood pressure. However, the level of the increased risk could not be determined and it was not possible to determine the crash risk for commercial drivers.(28)

Cognitive Impairment

Cognitive impairment in kidney disease may be caused by comorbid hypertension or anemia, or kidney disease treatments (including certain medications), and hemodialysis. The findings of some studies suggest that the severity of chronic kidney disease affects general cognitive function.(45,46) Factors such as higher serum creatinine, blood urea, uric acid P3 latency, and lower glomerular filtration rate, serum calcium, and hemoglobin with P3 latency have also been

associated with greater impairment.(46) In addition, advancing stages of chronic kidney disease (as categorized by GFR) were found to be associated with cognitive impairment.(45)

Dementia is common among patients with chronic renal failure, with point prevalence measured at 7.6 percent in patients not on hemodialysis and 7.0 percent in patients on hemodialysis.(28) These proportions are approximately three times that of the general population. Dementia in people with kidney disease is associated with advancing age, stroke, hypertension, anemia, and diabetes.(28)

Dementia has been associated with impaired driving. A meta-analysis that explored the relationship between neuropsychological functioning and driving ability in individuals with dementia concluded that driving ability tended to decline as cognitive functioning declined.(47) The tests discussed in the meta-analysis that demonstrated important relationships with on-road tests were in the visuospatial skills and attention/concentration cognitive domains. For non-road tests, mental status/general cognition, visuospatial skills, memory, and executive functions all demonstrated significant relationships. There were, however, limitations to the analysis. The drivers in the analysis had dementia, and variability in participant characteristics, data reporting, driving measures, and the widely held assumption that driving tests are valid and reliable for indicating driving ability, mean that the findings may not be generalizable to drivers with neurocognitive impairment less severe than dementia. The study does, however, provide some substantiation that mental impairment can increase the risk of crash.

Cerebrovascular Disease

The incidence of stroke in people of any age is 15.1 percent for patients on hemodialysis, 9.6% in patients with chronic kidney disease who are not on hemodialysis, and 2.6 percent in the general population. This means that the incident stroke rate of people on hemodialysis is five times that of the general medical population.(28) Post- stroke, chronic kidney disease patients are 20 percent more likely than people without the disorder.(28) Stroke is most likely to occur in the first year of hemodialysis.(28) Silent cerebral infarctions are also a concern for patients with chronic ESRD on hemodialysis because they are associated with high mortality.(48) Predictors of silent cerebral infarction such as hepatocyte growth factor (which increases with renal dysfunction) are currently being investigated.(48) Serum creatinine concentration has been identified as a possible risk factor for stroke. Patients in one study who had minor elevations in serum creatine but were still within normal limits (i.e. did not have kidney disease) were at increased risk for stroke.(49)

Cerebral microbleeds have been found to be more common in individuals with ESRD on hemodialysis. In one study, 35 percent of 80 patients with ESRD were found to have cerebral microbleeds.(50) Old bleeds were also identified on magnetic resonance imaging, however, the

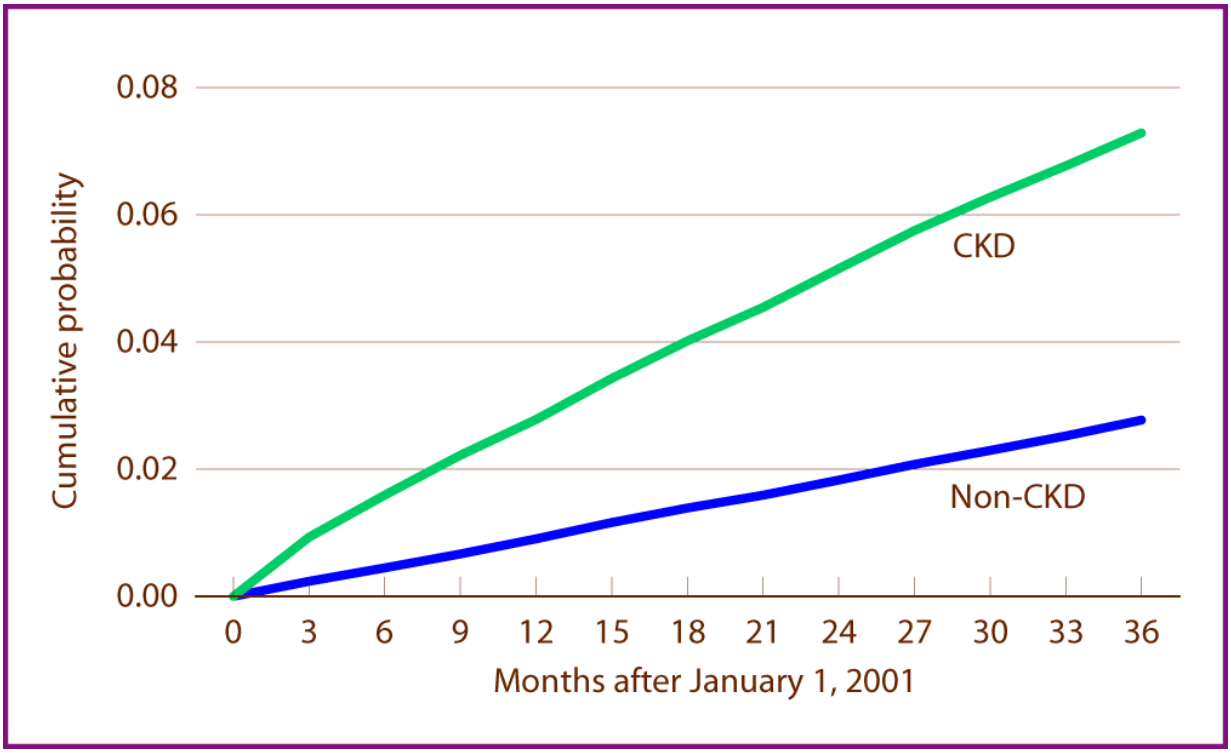
study authors suggested that chronic hypertension comorbid with kidney disease may actually account for the findings.

The high risk of cerebrovascular disease among patients with chronic kidney disease compared with the general population is important to driving because cerebrovascular disease and events have been associated with an increased risk of crash. In a study of assignment of culpability among 7,750 consecutive drivers of with complete records who crashed and were admitted to a hospital for their injuries, drivers with cerebrovascular disease were nearly twice as likely (Odds ratio [OR] 1.94 95 percent CI 1.20 to 3.28) to be considered at fault for their crash than all drivers in the sample.(41) Another study of 475 older drivers who crashed also found the odds summary estimate of at-fault crash among drivers with stroke was nearly double, though the analysis did not rule out the possibility that drivers with stroke were no more likely to cause crash than drivers without stroke (OR 1.9 (95 percent CI 0.9 – 3.9).(51)

Cardiovascular Disease

The prevalence of cardiovascular disease and incidence of related mortality is substantially higher in patients with kidney disease than in the general population. This is especially true for younger adults. In one study, the rate of death caused by cardiovascular disease of people aged 25 to 34 was 500-fold greater in patients with ESRD compared with matched controls in the general population.(52) Among older patients, the difference remains substantial, however, it is less dramatic (see Figure 2). A narrative review of other studies reported a 10- to 30-fold increase in death caused by cardiovascular disease, and 5- to 15-fold increase in myocardial infarction among dialysis patients of any age compared with the general population.(53) Even mildly reduced GFR has been associated with an increased risk of cardiovascular events and related death.(54)

Figure 2. Probability of Cardiac Arrest Among Older People With and Without Chronic Kidney Disease (CKD)



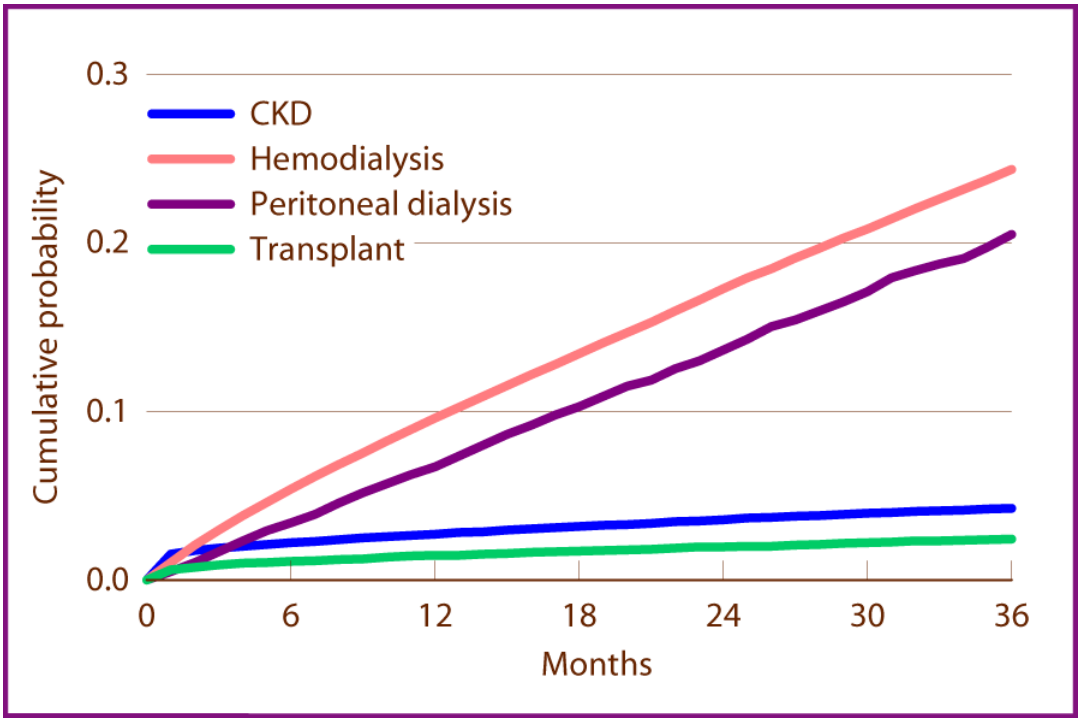
From the 2007 USRDS Atlas. Their caption: *General Medicare patients continuously enrolled in Medicare Parts A & B in 2000, age 65 & older on January 1, 2000; adjusted for age, gender, & ethnicity. Kidney disease defined in 2000.(28)*

Patients with ESRD who require dialysis are particularly vulnerable to cardiovascular disease, as most already have cardiovascular disease by the time they require dialysis. By the time dialysis is initiated, 80 percent of chronic kidney disease patients have developed left ventricular hypertrophy.(28) In addition, patients on dialysis are more susceptible to thromboses.(55) As shown in Figure 3, patients on either hemodialysis or peritoneal dialysis are at a substantially higher risk of sudden cardiac death than patients with chronic kidney disease or kidney transplant. This risk of cardiac arrest also increases with advanced age and in people with diabetes.(28) For reasons that are poorly understood, African Americans may be at greater risk than Caucasians.(56)

Overall, atherosclerotic cardiovascular disease is responsible for about half the deaths of all patients with ESRD.(57) About 27 percent of all-cause mortality in dialysis patients is attributed to arrhythmic mechanisms leading to sudden death.(28) Within the first 18 months of chronic renal failure onset or initiation of dialysis, approximately 11 to 12 percent of patients develop an acute myocardial infarction(28), and about 15 percentt of all cardiovascular deaths in patients on dialysis are attributed to myocardial infarction.(28) Cardiovascular disease can also take a chronic course. Within the first 18 months of diagnosis or beginning dialysis, 56 percent of chronic kidney disease patients develop congestive heart failure. Individuals with chronic kidney

disease who are not on dialysis also have a high probability of cardiac arrest (24 percent within three years).(28) Ischemic heart disease and left ventricular hypertrophy (even when systolic function is maintained) appear to be related to arrhythmia-related mortality and cardiomyopathy and cardiac arrest in patients with chronic renal failure.(28)

Figure 3. Probability of Cardiac Arrest in Incident Patients, Overall



From the 2007 USRDS Atlas. Their caption: *ESRD: incident Medicare dialysis and first transplant patients with Medicare as primary payor, age 20 and older, 2000–2002 combined. General Medicare (5 percent sample): incident kidney disease patients, age 66 & older, enrolled in Medicare for at least one year, 2000–2002 combined. Unadjusted for overall probabilities. In figures by age, gender, ethnicity, & diabetic status, data by one variable are adjusted for the remaining three; data by comorbidity are adjusted for age, gender, ethnicity, and diabetic status.*(28)

Some individuals on dialysis may be more susceptible to cardiovascular disease than others. Among dialysis patients, the relative risk of coronary artery disease increases with age, and has been found to be greater in men than women, in anemic patients, in obese patients, and in patients with increased levels of homocysteine.(58)

The high rate of cardiovascular disease among people with chronic kidney disease may be due in part to common risk factors shared by cardiovascular disease and chronic kidney disease, including advanced age, diabetes, and hypertension. Complications of kidney disease can also be risk factors for cardiovascular disease. These nontraditional risk factors for cardiovascular disease include anemia, inflammation, and abnormal calcium and phosphate metabolism.(59) In addition, 80 percent of patients starting dialysis have left ventricular hypertrophy.(28) However, shared risk factors do not entirely account for the relationship between chronic kidney disease and cardiovascular disease. Glomerular filtration rate has been found to be an independent risk

factor for atherosclerotic cardiovascular outcomes in community populations(60) and among older people.(61)

Perhaps more important, chronic kidney disease appears to accelerate cardiovascular disease. Mechanisms include promotion of hypertension and dyslipidemia, elevation of inflammatory mediators, activation of renin-angiotensins system, and increases in promoters of calcification.(52) Arteriosclerosis and remodeling of large arteries is highly prevalent in chronic kidney disease patients, possibly owing to pressure overload (which results in wall hypertrophy and increased wall-to-lumen ratio) or flow overload (marked by increased arterial diameter and wall thickness).(62) The prevalence of cardiomyopathy, which can lead to heart failure and ischemic heart disease, is also increased among chronic kidney disease patients.(62) Cardiomyopathy may result from hypertension, arteriosclerosis, anemia, fluid overload, or arteriovenous fistulas.(62) The combination of hypertension, dyslipidemia, and diabetes is particularly dangerous for the development of endothelial dysfunction and the progression of arthrosclerosis.(52) Microalbuminuria has also been associated with cardiovascular mortality in patients with diabetic nephropathy who do not use insuIin.(63) Anemia has been associated with left ventricular hypertrophy in patients on dialysis.(64)

Identifying risk factors for cardiovascular events has proved more difficult in people with chronic kidney disease or failure than for the general population.(28,65) A poor understanding of prognostic factors for cardiovascular events may be because patients with chronic kidney disease are excluded from studies on cardiovascular disease.(43)

The high rate of comorbidity of cardiovascular disease with kidney disease is important because drivers with cardiovascular disease are more likely to crash. In an evidence report on the risk of motor vehicle crash among drivers with cardiovascular disease, crash risk was found to be 1.43 times greater (95 percent CI 1.11–1.84) than for comparable individuals without cardiovascular disease. No conclusions were possible regarding crash risk of CMV drivers.(66)

Sleep Disorders

Sleep apnea, restless legs syndrome, and periodic limb movement disorder—all conditions that result in reduced quantity and quality of sleep—occur in higher rates among people with ESRD than in the general population.(67) Not surprisingly, many people with kidney disease also report excessive daytime sleepiness. A recent literature review reported daytime sleepiness rates of 52 to 67 percent and insomnia rates of up to 50 percent among ESRD patients.(67) Unintentional napping during the day was self-reported by 52 percent of patients with ESRD treated with peritoneal dialysis.(68)

Sleep apnea, a common and particularly disruptive sleep disorder, is characterized by a reduction or cessation of breathing during sleep coupled with symptoms such as daytime sleepiness.(69,70) Obstructive sleep apnea (OSA) occurs as a consequence of repeated upper airway obstruction during sleep as a result of narrowing of the luminal respiratory passages.(70) There are many causes for upper airway obstruction, including anatomical variations, accumulation of fat around the upper airway, or alcohol or drug-induced relaxation of the upper airway. OSA is a relatively common disorder affecting approximately 12 million individuals in the United States, with approximately 4 percent of men and 2 percent of women in the United States suffering from symptomatic sleep apnea.(70-74) One review of the literature found the prevalence of sleep apnea exceeding 50 percent in people with ESRD on dialysis.(75)

The most obvious effect of sleep apnea is excessive daytime sleepiness. However, untreated OSA increases the risk of the following disorders:(69,70,72-74,76-79) hypertension, angina, right-sided heart failure (corpulmonale), myocardial infarction, arrhythmias (including severe bradycardias), dilated cardiomyopathy, excessive carbon dioxide levels (hypercapnia), diabetes , stroke, and sudden death.(69,70,72-74,76-79) Untreated or poorly treated sleep apnea may contribute to hypertension, which may in turn worsen renal function.(80) In addition, sleep apnea is also thought to play a role in the increased rate of cardiovascular events s among people with kidney disease, and to accelerate arthrosclerosis in people with ESRD.(67) Therefore, it may be important to treat sleep apnea in order to decrease the risk of developing the disorders mentioned above.

There are several possible causes of sleep apnea in people with chronic kidney disease or failure. Clearly, many patients with chronic kidney disease have the same risk factors as people without kidney disease who suffer from sleep apnea, such as obesity and use of certain medications. In addition, uremia may contribute to disordered sleep and daytime sleepiness by causing accumulation of ureic toxins and volume overload.(67) In addition, uremia may contribute to destabilized central ventilatory control and upper airway occlusion.(67) Insufficient dialysis, which may contribute to uremia, has been considered a possible contributory cause of sleep apnea.(67) Dialysis itself has also been considered a cause. One survey found that sleep quality decreased during the first year of dialysis.(81) Effects of hemodialysis buffers on ventilatory control has been suggested as a cause in hemodialysis patients.(82) However, sleep respiratory disorders, including apnea, have also been observed in high prevalence on patients on peritoneal dialysis.(68,83)

Sleep apnea, related daytime sleepiness, and other consequential conditions have the potential to increase the risk of motor vehicle crash. In a comprehensive evidence report, sleep apnea in both commercial and non-commercial drivers was linked to an increased risk of motor vehicle crash. The FMCSA Evidence Report, “Obstructive Sleep Apnea and Commercial Motor Vehicle Driver

Safety" reported that an increased risk of crash was observed among CMV drivers; however, because the the evidence base was small, the size of this increase could not be accurately determined. However, owing to unexplained differences among study findings, a precise rate could not be estimated, though the 95 percent confidence intervals suggest the odds ratio for crash risk among noncommercial drivers with sleep apnea ranges from 1.3 to 5.7.

Natural History and Outcomes

Chronic kidney disease is almost always progressive. The rate of progression depends on many factors. One of the most important is the underlying cause of kidney disease. A retrospective data review found that patients with chronic glomerulonephritis had the fastest rate of progressive disease, as measured by a decline in serum creatinine.(84) The author of another review reported that diabetic nephropathy, polycystic kidney disease, and glomerulonephritis tend to be more progressive than nephroangiosclerosis and interstitial nephropathy.(85)

Important factors that affect the rate at which kidney disease progresses include baseline level of renal function, hypertension, and proteinuria.(85) Changes in diastolic blood pressure have correlated with the rate of kidney disease progression; however, it is unclear whether changes in blood pressure affect renal function, or vice versa.(86) Regardless of the underlying cause or reason for progressive decreased function, more advanced kidney disease is associated with greater prevalence and severity of morbidity, including hypertension, neurological and mental impairments, and mortality.(87)

The vast majority of individuals with chronic kidney disease do not progress to ESRD or die from ESRD. Based on data from the U.S. Renal Data System (USRDS), researchers have estimated that less than 2 percent of patients with chronic kidney disease eventually require renal replacement therapy (dialysis or transplant).(88) However, lifespan among individuals with kidney disease is substantially shortened. Among people with ESRD, patients under the age of 30 have a 75 percent reduction in life expectancy, and patients aged 40 to 59 have an 80 percent reduction in life expectancy, compared with people without ESRD.(28) In an analysis of 27,998 patients with kidney disease stages 2 through 4, researchers found that death was a far more common outcome than renal replacement therapy for all stages over a five-year observation period. The five-year mortality rate for individuals with stage 2 kidney disease was 19.5 percent, stage 3 was 24.35 percent, and stage 4 was 45.7 percent. In contrast, the rate of progression to renal failure requiring renal replacement therapy initiation during the same period was 1.1 percent for patients in stage 2 kidney disease, 1.3 percent for stage 3, and 19.9 percent for stage 4.(88) A prospective cohort study of patients already on dialysis found that 45 percent of all patients enrolled had died by the end of the four-year follow-up.(89) The outlook for individuals with diabetic nephropathy combined with persistent proteinuria is similar; one longitudinal study reported median survival at only six to seven years.(26) Another longitudinal study on patients

with ESRD reported a median survival time of 50 months, a bit longer than four years.(90) Clearly, kidney disease patients die prematurely. However, the cause of death is not usually attributed to renal failure: the leading cause of death in individuals with ESRD is actually cardiovascular disease.

Epidemiology

Chronic kidney disease is a common affliction in the United States. An estimated 150 new cases of chronic ESRD per 100,000 people are diagnosed in the United States annually.(91,92) A total of approximately 20 million people in the United States. (about 1 in 9, or 11 percent) have chronic kidney disease, and about 300,000 people in the United States (about 1 in 500, or 0.2 percent) have chronic renal failure. The overall adjusted incident rate of ESRD is 339 per million.(28)

A variety of risk factors have been associated with chronic kidney disease and failure, including age, gender, and ethnicity. The median age of Caucasians at onset of ESRD is 68 years. This age of onset is higher than for African American, Hispanic, and Native American patients; each nonwhite racial group had a median age of 59 to 60.(28)

Epidemiological factors vary somewhat according to the primary cause of chronic kidney disease. Demographic characteristics of end-stage chronic kidney disease are listed by cause in Table 4. A greater proportion of overweight and obese adults have chronic kidney disease than ideal-weight adults. The prevalence of chronic kidney disease of any severity level among obese adults is 4.5 percent, while the prevalence of chronic kidney disease among ideal- weight adults is 2.9 percent.(34)

Table 4. Epidemiological Characteristics of Individuals With ESRD (2000–2004)

Primary diagnosis	Total number of patients	% Prevalent	Median age	% Male	Ethnicity			
					White	African American	Native American	Asian
All ESRD	2,175,198	100.0	58	55.2	61.3	31.9	1.3	4.2
Diabetes	777,101	36.7	61	51.1	1.2	31.0	2.4	3.9
Hypertensive/large vessel disease	515,902	24.4	63	58.8	47.1	47.6	0.5	3.9
Glomerulonephritis	341,124	16.1	49	60.7	65.7	25.7	1.2	6.4
Cystic/hereditary/congenital disease	142,410	6.7	51	58.3	84.1	12.2	0.6	2.3
Interstitial nephritis/pyelonephritis	97,140	4.6	56	54	80.1	14.7	0.8	3.5
Etiology uncertain	85,769	4.1	55	57.8	67.3	24.7	1.0	5.0
Secondary glomerulonephritis/ vasculitis	69,759	3.3	42	29.5	60.1	33.6	1.0	4.3
Miscellaneous conditions (including trauma, AIDS, sickle cell disease, postpartum failure)	67,022	3.2	52	60.2	63.1	33.1	0.5	2.2
Missing (not reported)	59,188	2.8	51	57.1	62.4	27.8	0.5	4.0
Neoplasms/tumors	19,783	0.9	67	61.3	76.2	20.8	0.7	1.5

From USRDS data on CMS population(28)

End Stage Kidney disease (ESRD) and Employment

The prevalence of ESRD varies by union status and across employment industries. Union-based employees have more than twice the prevalence of kidney disease than workers who do not belong to a labor union.(28) Of workers in the transportation, communications, and utilities industries, approximately 1.2 percent of union workers have kidney disease, 0.4 percent of all workers have both kidney disease and diabetes, 0.6 percent have both kidney disease and hypertension, and 0.2 percent have kidney disease and a combination of diabetes and hypertension.(28)

ESRD is associated with non-employment. The poor health of many patients with ESRD, and the fact that all individuals in the United States with ESRD qualify for Social Security benefits, may contribute to non-employment rates.(93) Decreased physical work capacity, as measured by muscle strength and cardiovascular strength, may also play a role in whether patients with ESRD may work.(94) Published estimates of employment rates among ESRD patients on dialysis in the United States range from 6.6 percent a year after beginning dialysis(93) to less than 30 percent.(95) It is not clear whether a difference in employment rate is associated with the type of dialysis (hemodialysis or peritoneal dialysis), nor is it clear whether there is a relationship between employment rate and the underlying cause of ESRD.(93,95) The studies found that unemployed chronic dialysis patients have less formal education than dialysis patients who continue to work. They also found that dialysis patients who believe that people on dialysis should work are more likely to be employed.(93,96) This has also been found to be true among kidney transplant recipients.(97)

The Treatment of Kidney disease

Kidney disease can be difficult to treat because of the high rates of associated comorbidity and complications. Treatment goals include slowing the rate of kidney disease progression, managing anemia and other complications, managing the underlying cause of ESRD, and preventing premature death from complications such as cardiovascular disease.(28,65)

Pharmacotherapy

Pharmacotherapy cannot cure kidney disease. The main goals of pharmacotherapy are to control factors that cause or contribute to kidney disease (e.g., hypertension, diabetes), treat symptoms and complications of kidney disease (e.g. pruritis), and enable renal replacement therapy (e.g., the use of immunosuppressants to prevent rejection of a kidney transplant). For patients with ESRD, medications alone typically provide inadequate therapy. Renal replacement therapy, such as dialysis or kidney transplant, is usually necessary for complication management and survival.

Some typical pharmacotherapeutic treatments for chronic kidney disease include:

- For hemodialysis patients:
  - Anticoagulants: Heparin, warfarin
  - Parenteral Vitamin D: Calcitriol and paricalcitol IV
  - Phosphate Binders (nonaluminum): Calcium acetate
- Following transplantation
  - Immunosuppressants:
    - Calcineurin inhibitors: Tacrolimus (more common), cyclosporine A
    - Antimetabolites: Mycophenolate mofetil (more common), azathioprine
    - Rapamycin
    - Corticosteroids
  - Antibody Induction: Interleukin-2 (IL-2)receptor antibodies
- To treat pruritis
  - Antihistamine: diphenhydramine
- To treat anemia
  - Erythropoietin
  - Iron
- To treat hypertension
  - Angiotensin converting enzyme (ACE) inhibitors
  - Beta blockers
  - Calcium channel blockers
  - Vasodilators
- To treat cardiovascular disease
  - Beta blockers
  - Lipid-lowering drugs: Atorvastin
- To treat diabetes, if applicable
  - Insulin
  - Oral hypoglycemic agents

Although pharmacotherapy is a necessary component of medical management of kidney disease, medications often cause adverse events and side effects. Side effects that may interfere with safe operation of a motor vehicle include cognitive impairment and sedation. For example, the antihistamines taken for pruritis symptoms by a patient with ESRD have been associated with impaired driving. Diphenhydramine (Benadryl) has been found to impair measures of driving ability such as braking time and consistent following distance in healthy test subjects during experimental road tests.(98-100) The anticoagulant warfarin, which people with kidney disease may require to prevent a cardiovascular or cerebrovascular event during dialysis, was studied in

a general population of elderly drivers in Canada and was not found to be associated with an increased rate of crash.(101) However, another assessment of driving records found that anticoagulants and ACE inhibitors were associated with an increased risk of at-fault crash involvement among elderly non-commercial drivers, while calcium channel blockers or vasodilators, which are also used to treat hypertension were not associated with increased crash risk.(102) To further complicate the matter, the impact of many drugs on driving ability among people with kidney disease may be different from those who do not have the disorder, primarily because many of these drugs are typically metabolized or excreted via the kidneys, which may change the drug action. As with other disorders, the use of polypharmacy increases the risk of adverse effects, particularly when considering drug–drug interaction.

Dialysis

In 2004 (the most recent year for which data are available), 309,269 people were receiving dialysis. The incident rate of dialysis in 2004 was 94,891 for hemodialysis and 6,686 for peritoneal dialysis.(28)

Dialysis is implemented when renal function has decreased by approximately 90 percent. Its purpose is to provide an artificial substitute for the failing kidneys, although it can only provide about 10 percent of normal renal function.(103) Therefore, while it may help to support life and reduce the symptoms associated with ESRD, it cannot be expected to completely resolve the effects of renal failure. Missing a dialysis session can be life threatening. In the absence of blood filtration, uremic toxins will build up, and fluid overload increases cardiovascular risk.(103)

Hemodialysis implements an extracorporeal machine called a dialyzer to remove toxins, salt, and water from the blood and then return the processed blood to the body. The dialyzer uses many very small tubules (about 200 microns in diameter) made of semipermeable membranes. On the outside, these tubules are surrounded by dialysate solution, which contains sodium, potassium, bicarbonate and acetate, and calcium. As blood flows through the tubules, blood wastes, including urea, diffuse across the sides of the tubules into the dialysate solution. Water and salt are removed from the blood as they are forced by hydraulic pressure to diffuse across the semipermeable membrane.(103) Blood is removed and returned to the patient by an arteriovenous fistula, which must be created surgically. Daily hemodialysis is typically logistically prohibitive, in large part because it is time consuming. A typical session takes three to five hours and must be repeated three times a week. Less common is the ‘nocturnal dialysis’ approach, which is conducted in eight-hour overnight sessions three times a week.(103)

Peritoneal dialysis, also known as continuous ambulatory peritoneal dialysis (CAPD) entails filling the peritoneal cavity with 2 to 2.5 L of electrolyte solution through a plastic catheter permanently implanted into the peritoneal cavity. The solution is left in the cavity for four to six

hours while toxins, salts, and water diffuse across the peritoneal membrane into the electrolyte solution. The electrolyte solution plus unwanted salts and toxins are then drained from the peritoneal cavity and the process is repeated.(103) The main advantage of peritoneal dialysis over hemodialysis is its convenience. Disruptive and time-demanding sessions at a dialysis center are not required because treatment may take place at home or work. In addition, because the dialysis is performed more frequently (several times throughout the day), buildup of toxins and excess fluids between sessions is not as dramatic as for hemodialysis. Despite the advantages, it has an important potential disadvantage when compared with hemodialysis—reduced survival time. A study of individuals using peritoneal dialysis, showed they did not survive as long as hemodialysis patients.(104) The reasons are not clear. However, it has been associated with hypoalbuminemia and does not appear to be caused by cardiac disease.(104)

Treatment with either type of dialysis is associated with conditions that may potentially affect the safe operation of a motor vehicle. Neurological complications associated with dialysis include dialysis dementia, dysequilibrium syndrome, aggravation of atherosclerosis, cerebrovascular accidents, hypertensive encephalopathy, Wernicke's encephalopathy, hemorrhagic stroke, and intracranial hypertension.(105) Hemodialysis patients may experience muscle atrophy and related weakness and impaired movement.(106) Among hemodialysis patients, impaired sleep is very common, affecting about 70 percent of all individuals using the therapy(81,107) As a consequence, fatigue and daytime sleepiness are also common among dialysis patients.(108)

Transplantation

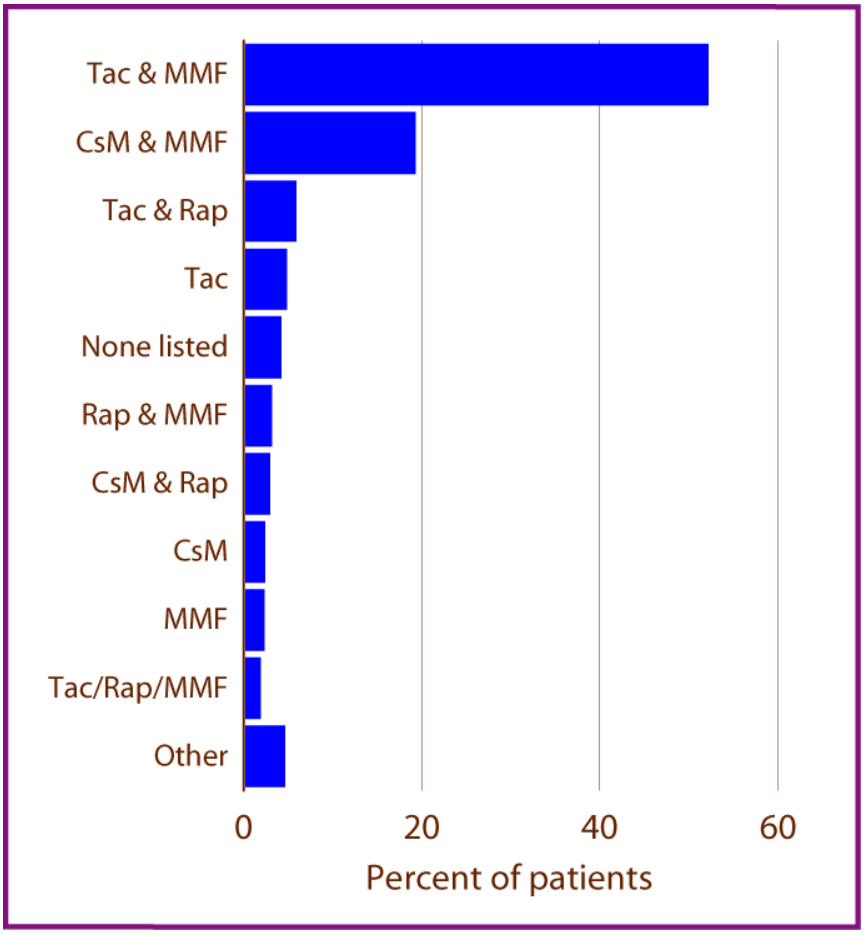
Kidney transplantation is the surgical implantation of a kidney harvested from a carefully matched cadaver or living donor into a patient with end-stage or borderline ESRD. Survival rates of kidney transplant recipients are high: 98 percent at one year and 91 percent at five years for living-donor recipients, and 95 percent at one year and 81 percent at five years for cadaver kidney recipients.(109) The most common cause of death during the first year following kidney transplantation is infection, followed by coronary artery disease.(109)

Despite high up-front costs, the favorable long-term outcomes associated with kidney transplantation make it cost effective.(110) However, the demand for donor kidneys far outweighs availability. In 2004, 60,993 patients were on the Organ Procurement and Transplantation (OPTN) list awaiting kidneys from deceased donors, but only 10,228 people received a transplant that year.(28) Since laparoscopic surgery became available to excise living donor kidneys, the popularity of living donation has increased. This form of donation, however, remains far less common than donations obtained from cadavers.(28)

The USRDS reports that post-transplantation immunosuppression drugs of choice have changed over the past 10 years. Tacrolimus has almost entirely replaced Cyclosporine A for baseline

calcineurin inhibitor use. Mycophenolate mofetil has replaced azathioprine for baseline antimetabolite use. Calcineurins and antimetabolites may be used concurrently. Interleukin-2 receptor antibodies and lymphocyte-depleting antibodies are also becoming more commonly used. Rapamycin is becoming a more commonly used maintenance immunosuppressant. At the same time, corticosteroid use is decreasing.(28) Figure 4 is a graphic of post-transplantation immunosuppression regimens.

Figure 4. Post-Transplantation Immunosuppression Regimens (2002–2004)



From the 2007 USRDS Atlas. Their caption: First-time, kidney-only transplants, 2002–2004. Maintenance immunosuppression as identified to OPTN [Organ Procurement and Transplantation Network].(28)

Although immunosuppressants make kidney transplantation possible, they do have potential complications, including acute femoral neuropathy, rejection encephalopathy, neuropathy in graft, neoplasms, myopathy, and progression of atherosclerosis.(105) Post-transplantation, individuals with severe kidney disease may be at higher than average risk for late venous thrombosis.(111)

Current Medical Fitness Standards and Guidelines for CMV Drivers in the United States

FMCSA regulations, found in 49 Code of Federal Regulations (CFRs) 301 through 399, cover businesses that operate CMVs in interstate commerce. FMCSA regulations that pertain to fitness to drive a commercial vehicle are found in 49 CFR 391 Subpart E. Only motor carriers engaged purely in intrastate commerce are not directly subject to these regulations. However, intrastate motor carriers are subject to state regulations, which must be identical to, or compatible with, the federal regulations in order for states to receive motor carrier safety grants from FMCSA. States have the option of exempting CMVs with a gross vehicle weight rating of less than 26,001 lbs.

Currently, there are no regulations that directly address CMV drivers with kidney disease. However, the current medical qualification standard for fitness to drive a CMV (49 CFR 391.41(b) subpart 5) states the following (see: http://www.fmcsa.dot.gov/rules-regulations/administration/fmcsr/fmcsrruletext.asp?section=391.41):

(a) A person shall not drive a CMV unless he/she is physically qualified to do so and, except as provided in §391.67, has on his/her person the original, or a photographic copy, of a medical examiner's certificate that he/she is physically qualified to drive a CMV.

The United States and Canada entered into a Reciprocity Agreement, effective March 30, 1999, recognizing that a Canadian commercial driver's license is proof of medical fitness to drive. Therefore, Canadian CMV drivers are no longer required to have in their possession a medical examiner's certificate if the driver has been issued, and possesses, a valid commercial driver's license issued by a Canadian Province or Territory. However, Canadian drivers who are insulin-using diabetics, who have epilepsy, or who are hearing impaired, as defined in §391.41(b)(11) are not qualified to drive CMVs in the United States. Furthermore, Canadian drivers who do not meet the medical fitness provisions of the Canadian National Safety Code for Motor Carriers but who have been issued a waiver by one of the Canadian Provinces or Territories are not qualified to drive CMVs in the United States.

Current Medical Qualification Guidelines

Currently, the FMCSA does not provide guidelines to medical examiners specific to the certification of individuals with kidney disease as being fit to drive a CMV.

Relevant Medical Fitness Standards and Guidelines from other U.S. Transportation Agencies

Current relevant medical fitness standards and guidelines for other U.S. transportation modes are summarized in Table 5. Included are pertinent rules and guidance for pilots, railroad workers,

and merchant mariners.

Table 5. Standards and Guidelines for Kidney disease from U.S. Government Transportation Safety Agencies

FAA* (all classes of airmen)	Railroad†	Merchant Mariner‡
GPO ACCESS Title 14: Aeronautics and Space 67.113 General medical condition. The general medical standards for a first-class airman medical certificate are: (a) No established medical history or clinical diagnosis of diabetes mellitus that requires insulin or any other hypoglycemic drug for control. (b) No other organic, functional, or structural disease, defect, or limitation that the Federal Air Surgeon, based on the case history and appropriate, qualified medical judgment relating to the condition involved, finds— (1) Makes the person unable to safely perform the duties or exercise the privileges of the airman certificate applied for or held; or (2) May reasonably be expected, for the maximum duration of the airman medical certificate applied for or held, to make the person unable to perform those duties or exercise those privileges. (c) No medication or other treatment that the Federal Air Surgeon, based on the case history and appropriate, qualified medical judgment relating to the medication or other treatment involved, finds— (1) Makes the person unable to safely perform the duties or exercise the privileges of the airman certificate applied for or held; or (2) May reasonably be expected, for the maximum duration of the airman medical certificate applied for or held, to make the person unable to perform those duties or exercise those privileges. § 67.401 Special issuance of medical certificates. (a) At the discretion of the Federal Air Surgeon, an Authorization for Special Issuance of a Medical Certificate (Authorization), valid for a specified period, may be granted to a person who does not meet the provisions of subparts B, C, or D of this part, if the person shows to the satisfaction of the Federal Air Surgeon that the duties authorized by the class of medical certificate applied for can be performed without endangering public safety during the period in which the Authorization would be in force. The Federal Air Surgeon may authorize a special medical flight test, practical test, or medical evaluation for this purpose. A medical certificate of the appropriate class may be issued to a person who does not meet the provisions of subparts B, C, or D of this part,if that person possesses a valid Authorization and is otherwise eligible. An airman medical certificate issued in accordance with this section shall expire no later than the end of the validity period or upon the withdrawal of the Authorization upon which it is based. At the end of its specified validity period, for grant of a new Authorization, the person must again show to the satisfaction of the Federal Air Surgeon that the duties authorized by the class of medical certificate applied for can be performed without endangering public safety during the period in which the Authorization would be in force. (b) At the discretion of the Federal Air Surgeon, a Statement of Demonstrated Ability (SODA) may be granted, instead of an Authorization, to a person whose disqualifying condition is static or nonprogressive and who has been found capable of performing airman duties without endangering public safety. A SODA does not expire and authorizes a designated aviation medical examiner to	The railroads have no specific medical standards addressing renal disorders.	Potentially disqualifying conditions listed in the Physical Evaluation Guidelines for Merchant Mariner's Documents and Licenses include any disease or constitutional defect that would result in gradual deterioration of performance of duties, sudden incapacitation or otherwise compromise shipboard safety, including required response in an emergency situation. Renal guidelines and standards include the following: GENITOURINARY (potentially disqualifying condition): Chronic renal failure GENERAL INFORMATION FOR MERCHANT MARINER'S DOCUMENTS, LICENSES, AND STCW CERTIFICATES REQUIRED MEDICAL INFORMATION A medical waiver from the Officer In Charge, Marine Inspection (OCMI) is required whenever a Merchant Mariner Physical Examination Report (CG-719K) reveals a medical condition that may affect your ability to perform the duties of the license or MMD applied for. Please provide a signed medical history statement from your doctor under his/her letterhead that includes the information below. STANDARD INFORMATION REQUIRED 1. The date on which the diagnosis was made. 2. A complete list of medications (current and past), including dosage and possible side effects. 3. Any limitations in the performance of your professional duties. 4. A prognosis of the potential deterioration or correction of your condition.

FAA* (all classes of airmen)	Railroad†	Merchant Mariner‡
issue a medical certificate of a specified class if the examiner finds that the condition described on its face has not adversely changed. (c) In granting an Authorization or SODA, the Federal Air Surgeon may consider the person's operational experience and any medical facts that may affect the ability of the person to perform airman duties including— (1) The combined effect on the person of failure to meet more than one requirement of this part; and (2) The prognosis derived from professional consideration of all available information regarding the person. (d) In granting an Authorization or SODA under this section, the Federal Air Surgeon specifies the class of medical certificate authorized to be issued and may do any or all of the following: (1) Limit the duration of an Authorization; (2) Condition the granting of a new Authorization on the results of subsequent medical tests, examinations, or evaluations; (3) State on the Authorization or SODA, and any medical certificate based upon it, any operational limitation needed for safety; or (4) Condition the continued effect of an Authorization or SODA, and any second- or third-class medical certificate based upon it, on compliance with a statement of functional limitations issued to the person in coordination with the Director of Flight Standards or the Director's designee. (e) In determining whether an Authorization or SODA should be granted to an applicant for a third-class medical certificate, the Federal Air Surgeon considers the freedom of an airman, exercising the privileges of a private pilot certificate, to accept reasonable risks to his or her person and property that are not acceptable in the exercise of commercial or airline transport pilot privileges, and, at the same time, considers the need to protect the safety of persons and property in other aircraft and on the ground. (f) An Authorization or SODA granted under the provisions of this section to a person who does not meet the applicable provisions of subparts B, C, or D of this part may be withdrawn, at the discretion of the Federal Air Surgeon, at any time if— (1) There is adverse change in the holder's medical condition; (2) The holder fails to comply with a statement of functional limitations or operational limitations issued as a condition of certification under this section; (3) Public safety would be endangered by the holder's exercise of airman privileges; (4) The holder fails to provide medical information reasonably needed by the Federal Air Surgeon for certification under this section; or (5) The holder makes or causes to be made a statement or entry that is the basis for withdrawal of an Authorization or SODA under §67.403. (g) A person who has been granted an Authorization or SODA under this section based on a special medical flight or practical test need not take the test again during later physical examinations unless the Federal Air Surgeon determines or has reason to believe that the physical deficiency has or may have degraded to a degree to require another special medical flight test or		

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practical test. (h) The authority of the Federal Air Surgeon under this section is also exercised by the Manager, Aeromedical Certification Division, and each Regional Flight Surgeon. (i) If an Authorization or SODA is withdrawn under paragraph (f) of this section, the following procedures apply: (1) The holder of the Authorization or SODA will be served a letter of withdrawal, stating the reason for the action; (2) By no later than 60 days after the service of the letter of withdrawal, the holder of the Authorization or SODA may request, in writing, that the Federal Air Surgeon provide for review of the decision to withdraw. The request for review may be accompanied by supporting medical evidence; (3) Within 60 days of receipt of a request for review, a written final decision either affirming or reversing the decision to withdraw will be issued; and (4) A medical certificate rendered invalid pursuant to a withdrawal, in accordance with paragraph (a) of this section, shall be surrendered to the Administrator upon request. (j) No grant of a special issuance made prior to September 16, 1996, may be used to obtain a medical certificate after the earlier of the following dates: (1) September 16, 1997; or (2) The date on which the holder of such special issuance is required to provide additional information to the FAA as a condition for continued medical certification The following is a partial list of conditions that warrant denial or deferral to the Aeromedical Certification Division, AAM-300. All disqualifying defects are subject to further FAA consideration. (See Item 48 for details concerning diabetes and Item 57 for other information related to the examination of urine). A. Urinary System 1. Calculus: renal, ureteral, or vesical (see 11 below). 2. Hydronephrosis with impaired renal function. 3. Nephrectomy, if associated with hypertension, uremia, infection of the remaining kidney, or other evidence of reduced renal function in the remaining kidney. 4. Nephritis: acute or chronic. 5. Nephrocalcinosis. 6. Nephrosis. 7. Polycystic kidney disease. 8. Pyelitis or pyelonephritis. 9. Pyonephrosis. 10. Tumors or malignancies, including prostatic carcinoma, require further evaluation. 11. Retained stones are disqualifying for issuance of a medical certificate. The Examiner should either deny or defer issuance and transmit the completed FAA Form 8500-8 to the Aeromedical		

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Certification Division. Complete studies to determine the possible etiology and prognosis are essential to favorable FAA consideration. Determining factors include site and location of the stones, complications such as compromise in renal function, repeated bouts of kidney infection, and need for therapy. Any underlying disease will be considered. The likelihood of sudden incapacitating symptoms is of primary concern. (See Item 18.j.).

12. Congenital lesions of the kidney are often benign, and certification of applicants with ectopic and horseshoe kidney, agenesis (unilateral), and even hypoplasia and dysplasia is possible.

13. Cystostomy and neurogenic bladder require evaluation by a specialist and deferral of certification to the Aeromedical Certification Division, AAM-300.

14. Glycosuria requires special evaluation. (Also see Items 48 and 57 for glycosuria associated with diabetes).

15. Renal dialysis and transplant are cause for denial. FAA certification may be possible after complete recovery from surgery and in limited circumstances involving dialysis.

Guide for Aviation Medical Examiners
Decision Considerations

Aerospace Medical Dispositions
Item 41. Genitourinary System - General Disorders

Disease/Condition	Class	Evaluation Data	Disposition
Congenital lesions of the kidney	All	Submit all pertinent medical information and status report	If the applicant has an ectopic, horseshoe kidney, unilateral agenesis, hypoplastic, or dysplastic and is asymptomatic – Issue Otherwise – Requires FAA Decision
Cystostomy and Neurogenic bladder	All	Requires evaluation, report must include etiology, clinical manifestation and treatment plan	Requires FAA Decision
Renal Dialysis	All	Submit a current status report, all pertinent medical reports to include etiology, clinical manifestation, BUN, Ca, PO^4,Creatinine, electrolytes, and treatment	Requires FAA Decision

FAA* (all classes of airmen)	Railroad†	Merchant Mariner‡
Guide for Aviation Medical Examiners Decision Considerations Disease Protocols Kidney transplant An applicant with a history of kidney transplant must submit the following if consideration for medical certification is desired: 1. Hospital admission, operative report and discharge summary 2. Current status report including: ○ The etiology of the primary kidney disease ○ History of hypertension or cardiac dysfunction ○ Sequela prior to transplant ○ A comment regarding rejection or graft versus host disease (GVHD) ○ Immunosuppressive therapy and side effects, if any ○ The results of the following laboratory results: CBC, BUN, creatinine, and electrolytes Guide for Aviation Medical Examiners Special Issuances AME Assisted - All Classes Renal Calculi AME Assisted Special Issuance (AASI) is a process that provides Examiners the ability to reissue an airman medical certificate under the provisions of an Authorization for Special Issuance of a Medical Certificate (Authorization) to an applicant who has a medical condition that is disqualifying under Title 14 of the Code of Federal Regulations (14 CFR) part 67. An FAA physician provides the initial certification decision and grants the Authorization in accordance with 14 CFR § 67.401. The Authorization letter is accompanied by attachments that specify the information that the treating physician(s) must provide for the reissuance determination. If this is a first time issuance of an Authorization for the above disease/condition, and the applicant has all the requisite medical information for a determination, the Examiner must defer and submit all of the documentation to the AMCD or RFS for the initial determination. Examiners may reissue an airman medical certificate under the provisions of an Authorization, if the applicant provides the following: An Authorization granted by the FAA; A statement from your treating physician regarding the location of the retained stone(s), estimation as to size of stone, and likelihood of becoming symptomatic; and A current report of appropriate imaging study (IVP, KUB, Ultrasound, or Spiral CT Scan) and provide a metabolic work-up, both performed within last 90 days.		

FAA* (all classes of airmen)	Railroad†	Merchant Mariner‡
The Examiner must defer to the AMCD or Region if: the treating physician comments that the current stone has a likelihood of becoming symptomatic; the retained stone(s) has moved when compared with previous evaluations; or the stone(s) has become larger when compared with previous evaluations. AME Assisted - All Classes Renal Carcinoma AME Assisted Special Issuance (AASI) is a process that provides Examiners the ability to reissue an airman medical certificate under the provisions of an Authorization for Special Issuance of a Medical Certificate (Authorization) to an applicant who has a medical condition that is disqualifying under Title 14 of the Code of Federal Regulations (14 CFR) part 67. An FAA physician provides the initial certification decision and grants the Authorization in accordance with 14 CFR § 67.401. The Authorization letter is accompanied by attachments that specify the information that treating physician(s) must provide for the reissuance determination. If this is a first time issuance of an Authorization for the above disease/condition, and the applicant has all the requisite medical information for a determination, the Examiner must defer and submit all documentation to the AMCD or RFS for the initial determination. Examiners may reissue an airman medical certificate under the provisions of an Authorization, if the applicant provides the following: An Authorization granted by the FAA; and A current status report performed within 90 days that must include all the required follow-up items and studies as listed in the Authorization letter and that confirms absence of recurrent disease. The Examiner must defer to the AMCD or Region if: There has been any recurrence of the cancer; or Any new treatment is initiated.		

*Source of information for FAA Regulations and Guidelines: http://www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/app_process/exam_tech/item41/amd/gd/

http://www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/app_process/exam_tech/item55/et/

http://www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/special_iss/all_classes/renal_cancer/

http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&sid=214deb5c74f0994cf7d0d3d3fa584802&rgn=div8&view=text&node=14:2.0.1.1.5.5.1.1&idno=14

†Source of information for Federal Railroad Administration Guidelines: http://www.fra.dot.gov/downloads/safety/hazmatch4.pdf

‡Source of information for Merchant Mariner Guidelines:

http://www.uscg.mil/hq/g-m/nvic/2_98/n2-98.pdf

http://www.uscg.mil/stcw/st-info-packs/General_Package.pdf

Relevant Medical Standards and Guidelines from Other Countries

Internationally, standards have been established to assess and determine the fitness of CMV drivers. Table 6 outlines regulatory standards and guidance pertaining to renal disorders and CMV driving in Australia, Canada, European Union, India, Ireland Kingdom of Bahrain, Malta, New Zealand, People's Republic of China, Singapore, United Kingdom, and Sweden.

Distinct worldwide policies by categories include:

Kidney Transplant

- *Australian, Canadian, and Swedish* guidelines allow CMV drivers a license after "successful" kidney transplant

Serious and Irreversible Renal Deficiency

- *European Union member states* will not issue or renew a CMV license

Advanced Chronic Renal Failure

- *Australian* guidelines suggest a conservative or restrictive approach to allow CMV driving
- *United Kingdom* authorities assess drivers individually

ESRD

- *New Zealand* authorities propose regular assessments may be imposed
- If drivers possess adequate cognitive and sensory motor ability, they are allowed to drive in *Canada*
- Dialysis is grounds for denial in *Sweden*

Hemodialysis

- CMV drivers are assessed individually in the *United Kingdom*
- *Canadian* authorities suggest that hemodialysis is typically not a feasible treatment approach for a long-distance driver

Table 6. Medical Standards and Guidelines for Kidney disease for Select Countries

Country	Reference	Guidelines
Australia	Assessing Fitness to Drive (For Commercial and Private Vehicle Drivers) Medical Standards for Licensing and Clinical Management Guidelines. Austroads and NTC (National Transport Commission) Australia (2006)	18.2 General Management Guidelines 18.2.1 Successful *kidney transplantation* reverses most of the metabolic or functional impairment of chronic renal failure, including those likely to be relevant to the driving task, and (after the initial post operative recovery) persons with kidney transplants who have good renal function are not regarded as impaired from a driving fitness point of view for private or CMVs. 18.2.4 The combination of the subtle cognitive impairment, probably present in most patients with *advanced chronic renal failure*, together with comorbidities associated with *renal failure* and *dialysis*, suggests a conservative/restrictive approach in the high-risk situation of commercial vehicle driving. 18.3 Medical Standards for Licensing: *Renal Failure* The criteria for an unconditional license are NOT met: • If the person has ESRD (requiring dialysis) or advanced pre-dialysis renal failure (GFR <20% of normal) A conditional license may be granted by the Driver Licensing Authority, taking into account the opinion of a renal specialist, and the nature of the driving task, and subject to periodic review: • If the patient's condition is stable with limited comorbidities
Canada	Determining medical fitness to Operate Motor Vehicles. CMA (Canadian Medical Association) Driver's Guide 7th edition. (2006)	Section 18/Kidney diseases *18.2 Dialysis* Patient with ESRD maintained on hemodialysis or peritoneal dialysis can drive any class of motor vehicle, provided they possess adequate cognitive and sensorimotor ability. All commercial drivers must be under the supervision of a nephrologist or an internist and have an annual medical review. Commercial drivers must be able to receive appropriate dialysis therapy while performing their work. For patients undergoing *peritoneal dialysis*, adequate supplies and an appropriate physical environment for exchanges must always be available. *Hemodialysis* is generally not a feasible treatment modality for a long-distance driver. If a commercial driver is planning to travel significant distances from home, unexpected delays due to weather, highway conditions, or demands of their work must be considered to ensure that dialysis treatments are not missed. *18.3 Kidney transplant* Drivers who have had a successful kidney transplant and who have fully recovered from surgery may drive any class of motor vehicle.
United Kingdom	At-a-glance Guide to the Current Medical Standards of Fitness to Drive (for Medical Practitioners) Issued by Drivers Medical Group. DVLA, Swansea (February 2007)	Chronic renal failure including *CAPD* (continuous ambulatory peritoneal dialysis) and *Hemodialysis*: Drivers with these disabilities will be assessed individually by DVLA Medical Unit All other renal disorders: Need not notify DVLA unless associated with significant symptoms or a relevant disability.
New Zealand	Medical aspects of fitness to drive: A Guide for Medical Practitioners. Land Transport Safety Authority. (May 2002)	10.3 Renal conditions In general, the presence of renal disorders does not normally constitute a problem with respect to safe driving unless end-stage renal failure or other complications have developed. For commercial license classes and endorsement types license condition for regular assessment may be imposed.

Country	Reference	Guidelines
European Union	European Commission on Transport and Road Safety, Annex III to Directive 91/439/EEC; Council Directive 96/47/EC July 1996 amending Directive 91/439/EEC; IP/06/381 Member States Agree on the European Driving License 27 March 2006 ▪ Countries involved include: Austria*, Belgium, Denmark, Finland*, France, Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Sweden*, , Portugal, Spain, and The United Kingdom (29 July 1991) ▪ Member states had to apply directive 91/439/EEC by 1 July 1996. ▪ European member states have to stay within a Council directive: they can be more restrictive, but not more liberal. *added in Council Directive 96/47/EC July 1996	Save in exceptional cases duly justified by authorized medical opinion, and subject to regular medical check-ups, driving licenses shall not be issued to or renewed for applicants or drivers suffering from *serious and irreversible renal deficiency*.
Sweden	Swedish National Road Administration (1999) Chapter 9: Renal Disorders	*General* 1. Seriously impaired function of the kidneys implying a danger to traffic safety constitutes grounds for denial of possession. 2. Regarding possession in Group 2, due consideration shall be given to the additional risks and dangers to traffic safety involved in such possession. *Dialysis Treatment* 1. The requirement of dialysis treatment constitutes grounds for denial of possession in Group 2 *Reappraisal* 1. A reappraisal shall occur at intervals considered suitable in each individual case. This also applies after a *kidney transplant*. *Medical Certification* A medical certificate shall be attached to the application for a learner's permit for Group 2. The certificate shall include a medical statement on whether or not the applicant suffers from a disease that implies a danger to traffic safety. In the case of renal disorders, including kidney transplant, a certificate must be issued by a specialist in internal medicine.
Ireland	Irish Statute Book, Statutory Instruments, S.I. No. 340/1986—Road Traffic (Licensing of Drivers) (Amendment) (No. 2) Regulations, 1986	In the case of an applicant for a license to drive a vehicle of any class, fitness to drive shall not be certified where the applicant suffers from *severe renal deficiency*.
India	Government of India The Motor Vehicle Act, 1988 Delhi Traffic Police FAQs related to Disabilities and Driving Driver Checkup; Ideal Proforma for a driver's health report	Before someone can start driving: ensure that you have obtained a written medical clearance to drive from a doctor or specialist. If the licensing authority has reasonable grounds to believe that the holder of the driving license is, by virtue of any disease or disability, unfit to drive a motor vehicle and where the authority revoking a driving license is not the authority that issued the same, it shall intimate the fact of revocation to the authority that issued that license.
Malta	Malta Transport Driving License	If, after you obtain a license, you develop a medical condition or any medical condition you may have worsens, it is your responsibility to inform the Licensing and Testing Directorate. These include but are not restricted to reporting medical conditions that may affect your driving ability.
People's Republic of China	Law of the People's Republic of China on Road Traffic Safety (Order of the President No.8) Chapter 2, Article 22	A person who suffers from a disease that prevents him/her from driving a motor vehicle safely, or cannot drive safely owing to over-fatigue shall not drive a motor vehicle.

Country	Reference	Guidelines
Singapore	Singapore Road Traffic Act	On an application for the grant of a driving license, the applicant shall make a declaration in the prescribed form as to whether or not s/he is suffering from any such disease or physical disability as may be specified in the form or any other disease or physical disability that would likely cause the driving of a motor vehicle, being a motor vehicle of such a class or description as authorized by the license to drive, to be a source of danger to the public
Kingdom of Bahrain	General Directorate of Traffic and Licensing, Ministry of the Interior. Vehicle Driving License Article 231	Applicants must be free of any disability that would prevent them from driving. In case of any doubts, the officials in the Directorate of Traffic and Licensing refer them to the medical expert or the Public Security physician for examination and presentation of an official certificate proving that they are free of any disability that would prevent them from driving.

Relevant Regulatory Standards from U.S.

Individuals operating a CMV in interstate commerce are subject to guidelines set forth in 49 C.F.R. 391.41(b). CMV drivers operating within state borders are subject to intrastate guidelines adopted by U.S. states, are presented in Table 7.

Table 7. Medical Standards for Kidney disease for CMV Drivers by State

State	Reference	Requirements for Renal Disorders
ALABAMA	Alabama Department of Public Safety Motor Carrier Safety Unit/FAQ www.dps.state.al.us/public/highwaypatrol	Please refer to Federal Regulations 391.45 for persons who must be medically examined and certified. Please refer to Federal Regulations 391.43 for guidelines on obtaining a medical card.
ALASKA	Title 2 Administration Chapter 90 Driver Licensing and Safety Responsibility Article 6 Standards for Licensing of Drivers 2 AAC.90.440 Medical Standards	2(b) The department will not issue a commercial driver's license to a person with a disqualifying medical condition as defined by the 49 C.F.R. Part 391, Subpart E (Federal Motor Carrier Safety Relations), revised as of October 1, 2005. (d) The department will not issue a commercial driver's license to a person with a disqualifying progressive disease or condition as defined by 49 C.F.R. Part 391, Subpart E (Federal Motor Carrier Safety Regulations), revised as of October 1, 2005.
ARIZONA	Arizona State Legislature Chapter 8 Motor Vehicle Driver Licensing Article 5 Commercial Driver Licensing 28-3223. Original applicant; requirements; expiration; renewal examination	A. In addition to the requirements applicable to all driver license applicants, an original applicant for a class A, B, or C license is subject to the following requirements: 1. The applicant shall submit evidence of compliance with medical standards and requirements that the department adopts by rule.
	Article 4 General Licensing Provisions 28-3159. Restricted licenses	A. With good cause, the department may issue the following restricted driver license: 2. A class A, B, or C driver license that restricts the driver from operating: (b) A vehicle in interstate commerce, if the applicant is not subject to 49 Code of Regulations part 391
	Arizona Driver License Manual and Customer Service Guide Motor Vehicle Division D.O.T. Medical Examination Report Commercial Driver Fitness Determination	Health History Drivers completes this section, but medical examiner is encouraged to discuss with driver: Yes/No: Kidney disease, dialysis For any "Yes" answer, indicate onset date, diagnosis, treating physician's name and address, and any current limitation. List all medications (including over the counter) used regularly or recently.

State	Reference	Requirements for Renal Disorders
ARKANSAS	Arkansas Code Title 27. Transportation Chapter 23. Commercial Driver's License Also known as Arkansas Uniform Commercial Drivers License Act	No mention of medical qualifications
	Arkansas Dept. of Finance Administration Including CDL Driver's Examination Manual	No mention of medical qualifications
CALIFORNIA	Department of Motor Vehicles Medical Report for Commercial Driver's License (CDL) www.dmv.ca.gov/commercial/commercial.htm	A medical form completed by a U.S. licensed doctor of medicine (M.D.), osteopathy (D.O.), licensed physician assistant (P.A.), a nurse practitioner (N.P.), advance practice nurse, or chiropractor who is clinically competent to perform the medical examination, must be given to the DMV with your original application for a driver license or instruction permit. The medical form must be dated within the last 2 years and on a form approved by the Federal Highway Administration, the Federal Aviation Administration, DMV, or on the DMV Report of Medical Examination Report form DL 51 (examiners asked to refer to Federal Regulations 49 C.F.R. 391.41).
COLORADO	Revised statutes Division of Motor Vehicles Motor Carrier Services/Forms DOT Medical Form (CDL Drivers)	No mention of medical qualifications Medical Examination Report for Commercial Driver Fitness Determination. No additional explanation is listed.
CONNECTICUT	Department of Motor Vehicles www.ct.gov Obtaining a Commercial Driver's License/Documents required when appearing for CDL. Knowledge testing Connecticut Code Title 14 – Motor Vehicles Chapter 246/Section 14-44E	Physical examination by a physician dated within the last two years, reported on an Examination to Determine Physical Condition of Driver (form R-323) or a U.S. D.O.T. Medical Examiner's Physical Examination Form CO730, which meets D.O.T. requirements in 49 C.F.R. 391.41-391.49. Sec 14-44E. Limitations on issuance of commercial driver's license. Qualification standards. Waiver of skills test. Requirements for license endorsement to operate vehicle transporting hazardous materials. Commercial driver's instruction permit. (b) The commissioner shall not issue a commercial driver's license to any person who has a physical or psychobehavioral impairment that affects such person's ability to operate a CMV safely. In determining whether to issue a commercial driver's license in any individual case, the commissioner shall apply the standards set forth in 49 C.F.R 391.41, as amended, unless it is established that the person will operate such vehicle only in this state, in which case the commissioner shall apply the standards set forth in this chapter and in regulations adopted thereunder.
DELAWARE	Delaware Code Title 21 Motor Vehicles Chapter 47. Motor Carrier Safety-Responsibility	4702. Adoption of federal requirements – In general. (a) The State hereby adopts the following parts of the Code of Federal Regulations, Title 49, Chapter III, Subchapter B, except as modified by this chapter. Part 391.adopted pursuant to the Transportation Article of the U.S. Code (49 U.S.C. §101 et seq.).
	Commercial Driver's Manual Delaware – Version 2.0	Basic CDL License Requirements: - Able to obtain medical certification under the Federal Motor Carrier Safety Regulations (Part 391.41 – Physical Qualifications for Drivers)

State	Reference	Requirements for Renal Disorders
DISTRICT OF COLUMBIA	District of Columbia Municipal Regulation Title 18 Vehicle and Traffic Chapter 13 Classification and Issuance of Commercial Driver's Licenses	1327 Physical Qualifications and Examinations 1327.1 No person shall be issued a new or renewed commercial driver's license unless he or she is physically qualified and, except as provided in the Federal Motor Carrier Safety Regulations (FMCSR), 49 CFR 391.49, possesses an original of a medical examiner's certificate, not more than two (2) years old, reflecting that he or she is physically qualified to drive a commercial vehicle. 1327.2 A person shall be considered physically qualified to drive a motor vehicle if that person meets the requirements in 49 CFR 391. 1327.3 Except as otherwise provided in this section, a medical examination to determine an applicant's physical qualification to operate a CMV shall be performed by a licensed doctor of medicine. 1327.8 Any CMV driver whose ability to perform his or her normal duties has been impaired by a physical or mental injury or disease must be reexamined and submit the certification required by §1327.3.
FLORIDA	Florida Department of Highway Safety & Motor Vehicles www.hsmv.state.fl.us	CDL Medical Information linked to FMCSA web site Medical Advisory Criteria for Evaluation Under 49 CFR Part 391.41. CDL Medical Information/Medical Report Form "Medical Exam Report for Commercial Driver Fitness Determination"
	2006 Florida Statutes Title XXIII Motor Vehicles Chapter 322 Driver's Licenses	322.12 Examination of applicants. (4) The examination for an applicant for a commercial driver's license shall include an actual demonstration of the applicant's ability to exercise ordinary and reasonable control in the safe operation of a motor vehicle or combination of vehicles of the type covered by the license classification which the applicant is seeking. 322.59 Possession of medical examiner's certificate. (1) The department shall not issue a commercial driver's license to any person who is required by the laws of this state or federal law to possess a medical examiner's certificate, unless such person presents a valid certificate prior to licensure.
GEORGIA	Georgia Department of Driver Services Commercial Driver's License Rules Chapter 1 Commercial Driver's Licensing Requirements www.dds.ga.gov	1-1-.04 Minimum Physical Requirements Required to Obtain a Commercial Driver's License. Amended. (1) Applicants for a commercial driver's license must comply with minimum Federal requirements as set forth in 49 C.F.R. § 391.41 1-1-.05 Exemptions from Medical Requirements. (1) Operators of city, county, state, or federal vehicles are exempt from the medical requirements. (2) Drivers who operate on an occasional basis receive no compensation and are not involved in commercial enterprise. 1-1-.06 Driver Qualifications. Amended. In order to be eligible for issuance of a commercial driver's license, each applicant must: (4) Comply with the minimum federal standards as set forth in C.F.R. § 391.41

State	Reference	Requirements for Renal Disorders
	Georgia Department of Driver Services Application for Georgia Commercial Driver's License	Part 4. Medical Certification Medical Qualifications: Unless specifically exempted, you must possess a valid medical examiner's certificate in order to operate a CMV (49 CFR § 391.41). Government employees (e.g., federal, state, county, or city employees) while operating government owned vehicles are exempt from this medical requirement
	Georgia Department of Driver Services Forms and Manuals	Medical Examination Report for Commercial Driver Fitness Determination with accompanying 49 CFR 391.41 available
HAWAII	Hawaii Revised Statutes Title 17 Motor and other Vehicles Chapter 286 Highway Safety Part XIII Commercial Driver Licensing	§ 286-236 Commercial driver's license qualification standards. (a) No person shall be issued a commercial driver's license unless that person meets the qualification standards of 49 Code of Federal Regulations, Part 391, Subparts B and E (e) A commercial driver's instruction permit may be issued to an individual who holds a valid driver's license, meets the qualification standards of 49 Code of Federal Regulations, Part 391, Subparts B and E, and has passed the written tests required for the desired class of a commercial driver's license.
IDAHO	Commercial Driver's License Manual Idaho 2007 Itd.idaho.gov/dmv/driverservices/cdl_manual	1.4 How to Get a CDL You will be asked if you are subject to and in compliance with the requirements of Part 391 of the Federal Motor Carrier Safety Regulations (Qualifications of Drivers). These include the DOT medical card requirements. Information regarding who is subject to these requirements may be found in Section 13 of this manual. Section 13: Forms/General Qualifications of Driver Requirements Unless exempt, every person who operates a CMV in interstate, foreign or intrastate commerce is subject to the Qualifications of Driver Requirements. (Refer to Federal Motor Carrier Safety Regulations, 49 CFR 391.11 for exact wording) B. An individual is qualified to drive a commercial vehicle if he/she: 4. Carries a current medical examiner's certificate (DOT medical card) stating that he/she is physically qualified to drive a commercial vehicle. (391 Subpart E)
	Idaho Administrative Code IDAPA 11.13.01 Motor Carrier Rules	019. Carrier Safety Requirements 01. Adoption of Federal Regulations. Adoption of Federal Regulations 49 CFR Parts….and 390 through 399 are hereby adopted by reference. Whenever any one (1) of these federal regulations (except Section 391.11(b)(1) exempts intrastate carriers from any of their requirements, this Rule at IDAPA 11.13.01, "The Motor Carrier Rules," Section 019, removes that exemption and subjects the intrastate carrier to the same requirements. a. All interstate and foreign carriers and intrastate carriers, except those carriers listed in Subsection 019.01.b., subject to the safety authority of the Idaho State Police while operating in Idaho that transport passengers or property, must comply with 49 CFR Parts…and 390 through 399, and the law and rules of the state of Idaho (except 391.11(b)(1) for intrastate carriers).
ILLINOIS	Illinois Commercial Driver's License Study Guide cyberdriveillinois.com	Federal Motor Carrier Safety Regulations are listed in Table C, pgs 131-132

State	Reference	Requirements for Renal Disorders
INDIANA	Indiana Administrative Code Title 140 Article 7 Driver's License Division	Rule 3. Commercial Driver's Licensing 140 IAC 7-3-3 Applicant Sec. 3 (7) The applicant must pass a physical examination prior to applying for an initial commercial driver's license and every two (2) years thereafter. In fulfilling this requirement, the applicant must meet the guidelines outlined in section 6 of this rule. Proof of passage of the physical examination within two (2) years prior to application must be presented to the bureau at the time of any application for a commercial driver's license or endorsement. (11) The applicant shall be issued his commercial driver's license subject to any restrictions on his driving privileges at the time of application. 140 IAC 7-3-5 Learner's permit Sec. 5 (a) Any person who is a resident of Indiana may apply for a commercial driver's license learner's permit. The applicant must (3) meet all visual and physical examination requirements 140 IAC 7-3-6 Physical examination requirements Sec. 6. Every applicant or holder of a commercial driver's license must pass a physical examination described as follows: (1) For interstate operation, a physical examination as described by the U.S. Department of Transportation, 49 C.F.R. 391.43. (2) For intrastate operation, a physical examination as prescribed by the bureau.
	Indiana Department of Revenue Motor Carrier Services Division Commercial Driver's License Section	IDOR Physical Examination Instructions and Information for Physical Examination Forms of CDL Holders
IOWA	Iowa Code 2001 Section 321.188 Commercial driver's license requirements	1. Before the department issues, renews, or upgrades a commercial driver's license and in addition to the requirements of section 321.182, the license applicant shall do all of the following: (a) Certify whether the applicant is subject to and meets applicable driver qualifications of 49 C.F.R. part 391 as adopted by rule by the department.
	Iowa Code Section 321.449 Motor Carrier Safety Rules	1. A person shall not operate a commercial vehicle on the highways of this state except in compliance with rules adopted by the department under chapter 17A. The rules shall be consistent with the Federal Motor Carrier Safety Regulations promulgated under U.S. Code, Title 49, and found in 49 CF.R. pts. 390 – 399 and adopted under chapter 17A. 5.a.Notwithstanding other provisions of this section, rules adopted under this section concerning physical and medical qualifications for drivers of CMVs engaged in intrastate commerce shall not be construed as disqualifying any individual who was employed as a driver of CMVs engaged in intrastate commerce whose physical or medical condition existed prior to July 29, 1996.
	Iowa Commercial Driver's License in a Nutshell Iowa Department of Transportation November 2005 Certification for Commercial Driver's License	Applicants must notify the state of Iowa if: 1) I am subject to and meet the driver qualifications of 49 Code of Federal Regulations, Part 391.(Interstate) OR 2) I am subject to and meet the driver qualifications of 49 Code of Federal Regulations, Part 391, adopted pursuant to Iowa Code Sections 321.449 and 321.450. (Intrastate) OR 3) I am not subject to either of the above driver qualifications.(if exemptions apply)

State	Reference	Requirements for Renal Disorders
KANSAS	Motor Carrier Regulations of the Transportation Division of The State Corporation Commission of The State of Kansas June 30, 2006	82-4-3g. Qualifications of drivers 49 C.F.R. Part 391, as in effect on October 1, 2003, is hereby adopted
	Commercial Driver's Manual	No discussion of medical qualifications
KENTUCKY	Kentucky Legislature Kentucky Administrative Regulation Title 601 Transportation Cabinet Department of Vehicle Regulation	The federal requirements for the issuance of a commercial driver's license to a driver operating in interstate commerce include a certification that the driver meets the qualification requirements contained in 49 C.F.R. 391. The Federal Highway Administration does not require a person who operates entirely in intrastate commerce to be subject to 49 C.F.R. 391. He is subject, however to Kentucky driver qualification requirements in 601 KAR 1:005 the Transportation Cabinet adopted the majority of the driver qualification requirements of 49 C.F.R. Part 391 on both an interstate and intrastate commerce basis.
LOUISIANA	Louisiana Office of Motor Vehicles Web01.dps.louisiana.gov	FMCSA medical forms available
	Louisiana Revised Statutes Title 32 Motor Vehicles and Traffic Regulation	§403.4 Medical evaluation report required of persons driving a CMV A. A person applying for a Class "A", "B", or "C" commercial driver's license shall not have any physical or mental disability affecting the ability to exercise ordinary reasonable control in the operation of a CMV. Such person, unless exempted by the office of motor vehicles or by a rule or regulation, shall provide a current medical report, on a form approved by the office of motor vehicles, prepared by a duly licensed medical examiner, certifying that he is capable of exercising ordinary reasonable control in the operation of a CMV. Such person shall submit a valid medical report at every renewal and shall carry a current medical certificate on his person at all times when driving a CMV requiring either a Class "A", "B", or "C" commercial driver's license as defined herein.
MAINE	Maine Commercial Driver's License Manual	Covers vision requirements only
	Maine Statutes Title 29-A: Motor Vehicles Chapter 11: Driver's License Subchapter 1: General Provisions	1253. Commercial licenses 2. Compliance with federal law. The State must comply with the ….Federal Motor Carrier Safety Improvement Act of 1999….in issuing or suspending a commercial license. (Sec. 215. Medical Certificate states "The Secretary shall initiate a rulemaking to provide for a Federal medical qualification certificate to be made a part of commercial driver's licenses").
MARYLAND	Maryland Motor Vehicle Administration maryland.mva.com/resource/DL-171	Medical Examination Report for Commercial Driver Fitness Determination available
MASSACHUSETTS	Massachusetts Registry of Motor Vehicles	Medical Examination Report for Commercial Driver Fitness Determination available
MICHIGAN	Michigan Department of State michigan.gov	Medical Examination Report for Commercial Driver Fitness Determination available
MINNESOTA	Minnesota/Department of Transportation Office of Freight and Commercial Vehicle Operations Minnesota Trucking Regulations	Section 06 Physical Qualifications for Drivers (49 CFR §391.41 and 391.43) A person is not allowed to drive a CMV unless physically qualified to do so and carries in his or her possession a current, valid copy of a medical examiner's certificate (health card) showing he or she is qualified.

State	Reference	Requirements for Renal Disorders
MISSISSIPPI	Senate Bill 3042 2007 Regular Session This act shall take effect and be in force from and after July 1, 2007.	An act to amend sections 77-7-7 and 77-7-716, Mississippi Code of 1972, to exempt certain vehicles from regulation under the Mississippi motor carrier regulatory law of 1938; to provide that the state enacts the exemption allowed under federal regulations for intrastate commerce; and for related purposes. Section 3. Notwithstanding the provisions of this chapter to the contrary, Parts 390 through 397, Title 49, Code of Federal Regulations, shall not apply to CMVs operated in intrastate commerce to transport property that have a gross vehicle weight rating or gross combination weight rating of twenty-six thousand (26,000) pounds or less.
MISSOURI	Missouri Motor Carrier Servies Missouri Department of Transportation Medical Program	Medical Examination Report for Commercial Driver Fitness Determination available
MONTANA	Montana Department of Transportation Motor Carrier Services Division 2003-2005 Law Book Effective October 1, 2003	61-5-10. Records check of applicants – examination of applicants – cooperative driver testing programs. (4)(a).a resident surrendering a commercial driver's license issued by another jurisdiction shall successfully complete any examination required by federal regulations before being issued a commercial driver's license by the department. 61-5-112. Types and classes of commercial driver's licenses – classification – rulemaking – reciprocity agreements. (1) The department shall adopt rules that it considers necessary for the safety and welfare of the traveling public governing the classification of commercial driver's licenses and related endorsements and the examination of commercial driver's license applicants and renewal applicants. The rules must: (a) subject to the exceptions provided in this section, comport with the requirements of 49 CFR, part 383, and the medical qualifications of 49 CFR, part 391
NEBRASKA	Nebraska Administrative Code Title 291 – Nebraska Public Service Commission Chapter 3 – Motor Carrier Rules and Regulations	005 Safety Regulations 005.01 Minimum Qualifications: Each person driving a motor vehicle subject to Commission jurisdiction shall possess the following minimum qualifications, except as provided in Section 005.19: 005.01A: Sound physical and mental condition with no mental, nervous, organic, or functional disease or structural defect or limitation likely to interfere with safe driving.
NEVADA	Nevada Revised Statute	NRS 483.330 Examination of applicants 1. The Department may require every applicant for a driver's license, including a commercial driver's license issued pursuant to NRS 483.900 to 483.940, inclusive, to submit to an examination. The examination may include: Further physical and mental examination as the Department finds necessary to determine the applicant's fitness to drive a motor vehicle safely on the highways.

State	Reference	Requirements for Renal Disorders
NEW HAMPSHIRE	State of New Hampshire Office of Legislative Services Administrative Rules/Department of Safety Chapter Saf-C 1800 Commercial Driver Licensing	Part Saf-C 1803 Commercial Driver's License Application Requirements Each applicant shall furnish the following on form DSMV 312: (11) The following certified statements:: f. The applicant meets the federal driver qualifications and requirements for interstate commerce Part Saf-C 909 Medical Waiver Saf-C 909.02 Waiver A person who is not physically qualified to drive due to having physical deficiency, as listed in 49 CFR 391.41(b)(3)-(13), shall obtain a medical evaluation summary that includes the following: 1. Whether the impairment interferes with the driver-applicants ability to perform normal tasks associated with driving a CMV; 2. An assessment and medical opinion of whether the condition is likely to remain medically stable for the duration of the medical waiver, and; 3. A recommendation as to the period of time the medical waiver shall be valid, not to exceed 2 years.
NEW JERSEY	New Jersey Legislature Title 39 Motor Vehicles and Traffic Regulation	39:3019.11 Definitions relative to commercial driver's licenses. "Disqualification" means either: (b) A determination by the Federal Motor Carrier Safety Administration under the rules of practice for motor carrier safety contained in 49 C.F.R.s386, that a person is no longer qualified to operate a CMV under 49 C.F.R.s 391
	Commercial Driver's License Manual 2006 Edition/Requirements for Licensing in New Jersey	Under provisions of these regulations, initial commercial driver license applicants must meet the medical fitness standards and possess a medical examiner's certificate as outlined in Title 49 CFR 391:41.
NEW MEXICO	New Mexico Statutes	66-5-60. Commercial driver's license; qualifications; standards. A. The division shall not issue a commercial driver's license to a person unless that person is a resident of New Mexico and has passed a knowledge test and skills test for driving a CMV and for related endorsements, has passed a fitness test, and has satisfied any other requirements of the New Mexico Commercial Driver's License Act [66-5-52 NMSA 1978] 65-3-7 Qualifications of drivers C. The driver may adopt regulations pertaining to the qualification and disqualification of commercial motor carrier vehicle drivers including documentation thereof. The regulations shall include but not be limited to background and character, road testing and written examination, physical qualification, examination and waivers of certain physical defects.
NEW YORK	New York State Department of Motor Vehicles Federal Requirements for Commercial Driver's License (CDL) Applicants	Informs first-time CDL applicants about federal medical requirements

State	Reference	Requirements for Renal Disorders
	Commercial Driver's License (CDL) Certifications	When you apply for an original NYS Commercial Driver's License (Class A, B or C) or a renewal, you must certify that: You meet or do not meet the requirements of the Federal regulations in 49 CFR Part 391, which include a requirement for a medical examination. 49 CFR Part 391 Certification The federal regulations include a requirement that a commercial driver have a medical examination every two years and receive a Medical Examiner's Certificate.
	New York State Commercial Driver's Manual	1.3 Commercial Driver's License Requirements 1.3.4 Medical Requirement The federal government requires most CMV drivers to have a medical examination in order to detect physical or mental conditions that may affect your ability to operate a motor vehicle safely. The examination requirements are found in the U.S. DOT Federal Motor Carrier Safety Regulations under 49 CFR Part 391. You are exempt from needing a medical examiner's certificate if you: are a government employee at any level of government
NORTH CAROLINA	North Carolina Department of Transportation Division of Motor Vehicles	Commercial Trucking/License Eligibility/Requirements Medical and Physical Requirements To drive a CMV, you should be able-bodied and free of physical handicaps. You should not suffer from any physical disability that could reduce driver control.
	North Carolina Statutes www.ncga.state.nc.us	G.S.20-37.13 sets the age qualifications for a commercial driver's license The Division shall not issue a driver's license to any person when in the opinion of the Division such person is afflicted with or suffering from such physical or mental disability or disease as will serve to prevent such person from exercising reasonable and ordinary control over a motor vehicle while operating the same on the highways.

State	Reference	Requirements for Renal Disorders
	North Carolina Administrative Code Section .0800 – Safety Rules and Regulations	19A NCAC 03D .0801 Safety of Operation and Equipment The rules and regulations adopted by the US DOT relating to safety of operation and equipment (49 CFR Parts 390-397 and amendments thereto) shall apply to all for-hire motor carriers and all for-hire motor carrier vehicles, and all private motor carriers and all private motor carriers engaged in intrastate commerce over the highways of the State of NC, if such vehicles have a GVWR of greater than 26,000 pounds; …Provided the following exceptions shall also apply to all intrastate motor carriers: Persons who otherwise qualify medically to operate a CMV within the State of NC shall be exempt from the provisions of Part 391.11(b)(1) and may be exempt from provisions of Part 391.41(b)(1) through (11) where applicable and therefore shall be authorized for intrastate operation if approved by an Exemption Review Officer appointed by the Commissioner of Motor Vehicles. These drivers shall continue to be exempt upon completion of a medical examination indicating the condition has not worsened or no new disqualifying conditions have been diagnosed and upon continued approval of an Exemption Review Officer. After a medical review by the Exemption Review Officer, a driver may be granted a waiver not to exceed a period of two years based on the type and severity of the condition. The Exemption Review Officer shall follow the guidelines established for variances from the FMCSR for intrastate commerce found in 49 CFR, Part 350.341.
NORTH DAKOTA	Commercial Drivers License Guide 2005-2007	Medical Qualifications All commercial drivers must meet the federal commercial medical requirements in 49 CFR 391. To continue to be medically qualified to operate a CMV, you must be medically examined by a U.S. licensed health care provider every 24 months.
OHIO	Ohio Code	4506.10 Physical qualifications for commercial driver's license No person who holds a valid commercial driver's license shall drive a CMV unless the person is physically qualified to do so. Each person who drives or expects to drive a CMV in interstate or foreign commerce or is otherwise subject to 49 C.F.R. 391, et seq., as amended, shall certify to the registrar of motor vehicles at the time of application for a commercial driver's license that the person is in compliance with these standards.
OKLAHOMA	Oklahoma Administrative Code www.oar.state.ok.us Chapter 595, Department of Public Safety Chapter 10, Drivers Licenses and Identification Cards Subchapter 5, Medical Aspects	595:10-5-4. Applicability All Class A, B, or C commercial vehicle operators must meet the federal requirements set forth in 49 CFR §391 et seq.
OREGON	Oregon Administrative Rule	735-074-0260 Medical Standards for Drivers of CMVs The Driver and Motor Vehicle Services Division of the Department of Transportation (DMV) adopts the U.S. Department of Transportation regulations contained in 49 CFR 391.41 through 391.49 (2004) pertaining to physical qualifications and medical examination of drivers of CMVs.
PENNSYLVANIA	PA Public Utility Commission Motor Carrier Services and Enforcement Division	Safety Fitness Review Program Educational and Technical Assistance Package Part 391 – Qualifications of Drivers Motor carriers must ensure that all drivers meet the Physical Qualifications and Examinations required in Part 391.41 and possess a valid medical certificate.

State	Reference	Requirements for Renal Disorders
RHODE ISLAND	Rules and Regulations Governing Applicants for Commercial Driver's Licenses, Permits, Renewals and Endorsements Adopted 2007 Department of Revenue/Division of Motor Vehicles	Rule 3. Minimum Eligibility for Commercial Driver's License, Permit or Endorsement 3.2 At the time of submitting the application, the applicant must be physically qualified to safely operate a CMV. In making this determination, the Division of Motor Vehicles shall follow applicable federal guidelines contained in 49 C.F.R. § 391.41 and may seek recommendations from the Medical Advisory Board pursuant to Section 31-10-44 of the Rhode Island General Laws.
	Rhode Island Code	§ 31-10.3-19 – Examination of Applicants The department shall examine every applicant for a commercial driver's license. The examination shall include an actual demonstration of ability to exercise ordinary and reasonable control in the operation of a motor vehicle or combination of vehicles of the type covered by the license classification the applicant is seeking. The examination may also include any further physical and mental examinations the department deems necessary to determine the applicant's fitness to safely operate a motor vehicle on the highways.
SOUTH CAROLINA	CMV Manual	Transfer of Commercial Driver's License To transfer a CDL from another state to SC: Certify you have read and understand and meet the qualifications requirements under 49 CFR, Part 39 of the FMCSRs. You must also show a valid DOT physical card or long form.
SOUTH DAKOTA	South Dakota Code 49	49-28A-3 Adoption of federal regulations—Violation as misdemeanor. The state hereby adopts Title 49 of the Code of Federal Regulations, subtitle B, chapter III, subchapter B, parts 390 to 397, inclusive as amended through January 1, 2006, with the following modifications: (3) Intrastate drivers are exempt from the physical requirements of part 391.41
TENNESSEE	Rules of TN Department of Safety Division of Driver License Issuance Chapter 1340-1-13 Classified and Commercial Driver's Licenses and Certificates for Driving	1340-1-13.09 Mental and Physical Standards Applicants for commercial driver's licenses shall meet the minimum physical and mental standards set forth in 49 C.F.R. § 391.41 (1989), except for those specifically exempted therein who are not required to have the Passenger, School Bus, or Hazardous Materials endorsement. (2) Applicants for commercial driver's license involved only in intrastate commerce who do not meet the standards set forth in 49 § 391 (1989) may be eligible for special licenses restricting their operation of a CMV
TEXAS	Texas Administrative Code Title 37 Public Safety and Corrections Part 1 Texas Dept of Public Safety Chapter 16 Commercial Drivers License Subchapter A Licensing Requirements, Qualifications, Restrictions, and Endorsements	Rule 16.9 Qualifications to Drive in Intrastate Commerce (a) Persons who do not qualify to drive in interstate commerce may still qualify to drive in intrastate commerce. In such cases, the commercial driver's license (CDL) will contain an "M" restriction.

State	Reference	Requirements for Renal Disorders
UTAH	Utah Department of Public Safety Driver License Division	72-9-301. Duties-Enforcement-Federal safety regulations-Audits-Rights of entry for audits. (1) The department shall administer and in cooperation with the Department of Public Safety, Utah Highway Patrol Division, as specified under Section 53-8-105, shall enforce state and federal laws related to the operation of a motor carrier within the state, including: (e) the Federal Motor Carrier as contained in Title 49, Code of Federal Regulations
VERMONT	Vermont Statutes Title 23 Motor Vehicles Chapter 39: Commercial Driver License Act	4110. Application for commercial driver's license (A) for an applicant who operates or expects to operate in interstate or foreign commerce or who is otherwise subject to 49 C.F.R. part 391, the applicant meets the qualifications requirements contained in part 391. If the applicant operates or expects to operate entirely in intrastate commerce and is not subject to part 391, the applicant is subject to state driver qualification requirements and is not subject to part 391
	Department of Motor Vehicles CDL Manual	Physical Examination Requirements If you are subject to the Federal Motor Carrier Safety Regulations, you must have a physical examination every 2 years and carry the medical card at all times. To have a hazardous materials endorsement, you must meet the Federal Motor Carrier Safety regulations except for age requirements for intrastate travel.
VIRGINIA	Commonwealth of Virginia Department of Motor Vehicles Commercial Driver's Manual	Compliance with Motor Carrier Safety Regulations All CDL applicants must certify that they are in compliance with the federal or Virginia motor carrier safety regulations or that they do not have to comply with them.
	Virginia Code 46.2-341.12. Application for commercial driver's license	The applicant should provide the following: 2. Certifications that: s/he either meets the federal requirements of 49 C.F.R. Part 391, or s/he is exempt from or is not subject to such federal requirements
WASHINGTON	WA State Licensing: Commercial Driver Fitness Determination	All commercial drivers must meet the medical standards established by federal and state laws, rules, and regulations. Reference: FMCSR parts 391.41 and 391.49
WEST VIRGINIA	Commercial Driver's Manual	Age and Fitness Requirements Federal Motor Carrier Regulations (49 CFR Part 391.41) require that drivers subject to those rules meet specific physical qualification standards and carry evidence of such qualification in the form of a medical certificate. Note: all drivers are subject to FMSCR requirements (DOT medical) except for city, county, state, or federal employees.

State	Reference	Requirements for Renal Disorders
WISCONSIN	Department of Transportation Chapter Trans 112 Medical Standards for Driver Licensing and General Standards for School Bus Endorsements	Trans 112.08 Conditions affecting endocrine function (1) with respect to conditions affecting endocrine function, the review boards, when making recommendations, and the department when taking licensing action, may consider disorders including, but not limited to, the following: (e) adrenal dysfunction (2) The department may require information on a person's functional ability including, but not limited to, the following: (c) complications of condition (d) reliability of the person in following a prescribed treatment (e) weakness (f) fluid and electrolyte imbalance (g) mental changes (i) frequency of symptoms *(3)(a) Licensing standards.* No license or endorsement may be issued to, renewed by, or held by a person who does not meet the applicable medical review standards for conditions affecting endocrine functions of this subsection.
WYOMING	Wyoming Statutes Title 31 Motor Vehicles Article 3 Commercial Driver's License	31-7-304. Issuance; classifications, and endorsements. (f) Before issuing or renewing a commercial driver's license, the department shall require that the applicant present a current federal medical qualification certificate

Methods

The *Methods* section is a synopsis of how we identified and analyzed the information in this evidence report. It briefly covers the key questions addressed, literature searches performed, criteria used for including studies, evaluation of study quality, assessment of the strength of the evidence base for each key question, and methods used for abstracting and analyzing available data. Specific details of literature searches, study quality assessment, statistical approaches, and related topics are documented in appendices.

Key Questions

This evidence report addresses four key questions. These key questions, developed by the FMCSA in collaboration with Manila Consulting Group, are listed below:

Key Question 1: *Are individuals with kidney disease (any stage) at an increased risk for a motor vehicle crash*?

Key Question 2: *Are medications used to treat individuals with kidney disease associated with an increased risk of motor vehicle crash among pre-dialysis patients*?

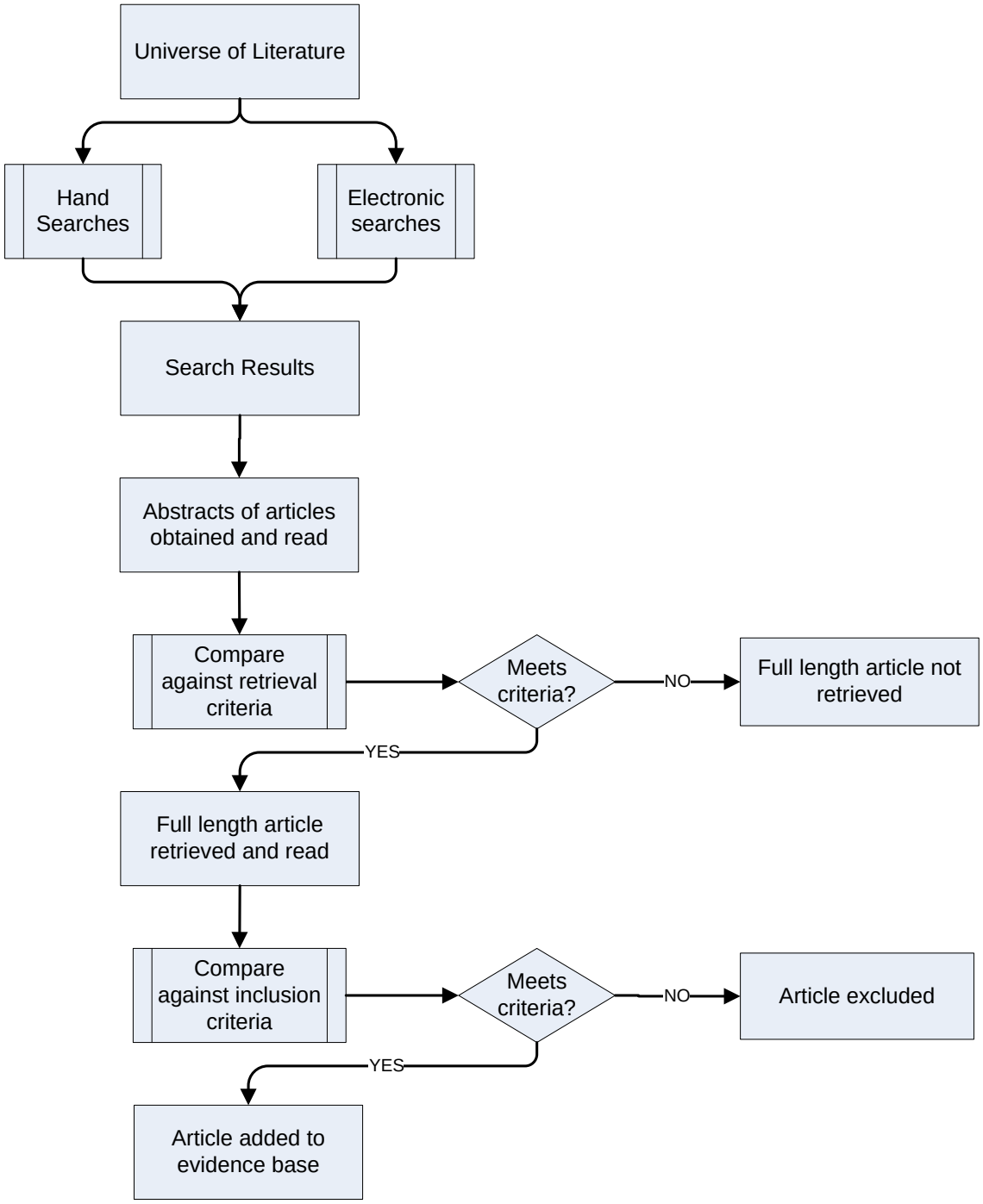
Key Question 3: *Are dialysis and accompanying drug treatments associated with an increased risk of motor vehicle crash*?

Key Question 4: *Are kidney transplantation and accompanying drug treatments associated with an increased risk of motor vehicle crash*?

Identification of Evidence Bases

The individual evidence bases for each of the four key questions addressed in this evidence report were identified using the multistage process captured by the algorithm in Figure 5. The first stage process consists of a comprehensive search of the literature. The second stage consists of the examination of abstracts of identified studies to determine which articles will be retrieved. The final stage consists of selection of the actual articles that will be included in the evidence base.

Figure 5. Evidence Base Identification Algorithm



Searches

One characteristic of a good evidence report is a systematic and comprehensive search for information. Such searches distinguish systematic reviews from traditional literature reviews that use a less rigorous approach to identifying and obtaining literature. This allows a reviewer to include only articles that agree with a particular perspective and to ignore articles that do not. Our approach precludes this potential reviewer bias, because we obtain and include articles according to explicitly determined *a priori* criteria. Details of the search strategies used in this report are in Appendix A.

Electronic Searches

We performed comprehensive searches of the electronic databases listed in Table 8.

Table 8. Electronic Databases Searched

Name of Database	Date Limits	Platform/Provider
CINAHL (Cumulative Index to Nursing and Allied Health Literature)	1982 through September 12, 2007	OVID
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	Through 2007 Issue 3	www.thecochranelibrary.com
Database of Abstracts of Reviews of Effects (DARE)	Through 2007 Issue 3	www.thecochranelibrary.com
The Cochrane Central Register of Controlled Trials (CENTRAL)	Through 2007 Issue 3	www.thecochranelibrary.com
The Cochrane Database of Methodology Reviews (Methodology Reviews)	Through 2007 Issue 3	www.thecochranelibrary.com
ECRI Institute Library Catalog	Through September 12, 2007	ECRI Institute
Embase (Excerpta Medica)	1980 through September 12, 2007	OVID
Health Technology Assessment Database (HTA)	Through 2007 Issue 3	www.thecochranelibrary.com
Healthcare Standards	1975 through September 12, 2007	ECRI Institute
International Health Technology Assessment (IHTA)	Through September 12, 2007	RI
Medline	1950 through September 12, 2007	OVID
National Guideline Clearinghouse (NGC)	Searched September 21, 2007	www.ngc.gov
NHS Economic Evaluation Database (NHS EED)	Through 2007 Issue 3	www.thecochranelibrary.com
PsycINFO	Through September 12, 2007	OVID
PubMed (Premedline)	Premedline[sb] Searched September 12, 2007	www.pubmed.gov

Manual Searches

We reviewed journals and supplements maintained in ECRI Institute's collections of more than 1,000 periodicals. Non-journal publications and conference proceedings from professional organizations, private agencies, and government agencies were also screened. In addition, we examined the reference lists of all obtained articles with to identify relevant reports not identified by our electronic searches. To retrieve additional relevant information, we performed hand searches of the "gray literature"—reports, studies, articles, and monographs produced by federal

and local government agencies, private organizations, educational facilities, consulting firms, and corporations. These latter documents do not appear in peer-reviewed journal literature.

Retrieval Criteria

Retrieval criteria were used to determine whether a full-length version of an article identified by our searches should be ordered. Decisions on whether a full-length article should be retrieved are usually based on a review of abstracts. For this project, retrieval criteria were determined *a priori* in conjunction with the FMCSA. The retrieval criteria are in Appendix B.

If an article did not meet the retrieval criteria for this evidence report, the full-length version of the article was not obtained. If it was unclear whether a potentially relevant article met our retrieval criteria (e.g., no abstract was available), the full-length version of that article was obtained.

Inclusion and Exclusion Criteria

Each retrieved article was read in full by an ECRI Institute analyst who determined whether that article met a set of predetermined, question-specific inclusion criteria. As was the case for the retrieval criteria, the inclusion and exclusion criteria for this evidence report were determined *a priori* in conjunction with the FMCSA. The inclusion and exclusion criteria are in Appendix C.

If, on reading an article, it was found not to meet the question–specific inclusion criteria listed in Appendix C, the article was excluded from the analysis. Each excluded article, along with the reason(s) for its exclusion, are listed in Appendix D.

Evaluation of Quality of Evidence

Rather than focus on the quality of the individual studies that comprise an evidence base, our approach to assessing the quality of evidence focuses on the overall *body* of the available evidence used to draw an evidence-based conclusion.(112) Using this approach, described briefly in Appendix E, we took into account not only the quality of the individual studies that comprise the evidence base for each key question, but also considered the interplay between the quality, quantity, robustness, and consistency of the overall body of evidence.

Our approach to assessing the strength of the body of evidence makes a clear distinction between a qualitative conclusion (e.g., individuals with kidney disease are at increased risk for a motor vehicle accident) and a quantitative conclusion (e.g., when compared with individuals without kidney disease, the relative risk for a motor vehicle crash among individuals with the disorder is 1.47 (95 percent CI: 1.03–1.74; $P<0.005$)). As shown in Table 9, we assign a separate strength-and-stability-of-evidence rating to each of type of conclusion. Evidence underpinning a

qualitative conclusion is rated according to its strength, and evidence underpinning quantitative conclusions is rated according to the stability of the effect–size estimate that is calculated.

Table 9. Strength-and-Stability-of-Evidence Ratings for Qualitative and Quantitative Conclusions

Strength of Evidence	Interpretation
Qualitative Conclusion	
Strong	Evidence supporting the qualitative conclusion is convincing. It is highly unlikely that new evidence will lead to a change in this conclusion.
Moderate	Evidence supporting the qualitative conclusion is somewhat convincing. There is a small chance that new evidence will overturn or strengthen our conclusion. ECRI Institute recommends regular monitoring of the relevant literature for moderate-strength conclusions.
Acceptable	Although some evidence exists to support the qualitative conclusion, this evidence is tentative and perishable. There is a reasonable chance that new evidence will either overturn or strengthen our conclusions. ECRI Institute recommends frequent monitoring of the relevant literature.
Unacceptable	Although some evidence exists, the evidence is insufficient to warrant drawing an evidence-based conclusion. ECRI Institute recommends frequent monitoring of the relevant literature.
Quantitative Conclusion	
High	The estimate of treatment effect in the conclusion is stable. It is highly unlikely that the magnitude of this estimate will change substantially as a result of the publication of new evidence.
Moderate	The estimate of treatment effect the conclusion is somewhat stable. There is a small chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI Institute recommends regular monitoring of the relevant literature.
Low	The estimate of treatment effect included in the conclusion is likely to be unstable. There is a reasonable chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI Institute recommends frequent monitoring of the relevant literature.
Unstable	Estimates of the treatment effect are too unstable to allow a quantitative conclusion to be drawn at this time. ECRI Institute recommends frequent monitoring of the relevant literature.

The definitions in the table above are intuitive. Qualitative conclusions supported by strong evidence are less likely to be overturned by the publication of new data than conclusions supported by weak evidence. Likewise, quantitative effect–size estimates deemed to be stable are less likely to change significantly with the publication of new data than unstable effect–size estimates.

Methodological Issues Specific to the Study of Kidney disease

One of the methodological challenges specific to the study of kidney disease is differentiating the effects of ESRD and treatments for ESRD. Since ESRD requires renal replacement therapy to sustain life, it is generally not possible to study untreated patients and compare them with treated patients (although we identified and included one small study that did this[113]). Therefore, we divided the evidence base up by stage of kidney disease and related treatment and assessed the evidence on medications and pre-dialysis (Stage 1 though 4) kidney disease separately in Key Question 2. In Key Question 3 we assessed risk of crash associated with ESRD requiring dialysis and related medications, and in Key Question 4 we did the same for transplant recipients.

Statistical Methods

Whenever possible, we use an extensive set of analytic techniques (see Appendix B for methods selected *a priori*). However, the limited quantity of evidence suitable for combination prevented us from attempting to form quantitative conclusions using meta-analysis in this report. Given these limitations, we found our best analytic approach was to evaluate each relevant finding from each included study and assess these findings using a qualitative approach.

We calculated several different estimates of effect. The choice of effect–size estimate depended on the purpose of the studies we assessed, their design, and whether reported outcome data were continuous or dichotomous. Between-group differences in outcome measured using continuous data were standardized into a common metric known as the standardized mean difference (SMD). For indirect evidence, which related to neurocognitive impairment or sleep-related disorders, we calculated SMDs and *p*-values from each study (except where noted as otherwise). We used these results in our outcome-by-outcome narration of the studies' findings. For direct evidence on risk of crash, we calculated two different estimates of effect. These dichotomous data were analyzed using the rate ratio (RR) or the odds ratio (OR).

The formulae for these effect sizes and their variance are in Table 10.

Table 10.Effect-size Estimates Used in Evidence Report and their Variance

Effect size	Formula (Effect size)	Formula (Variance)
SMD	$\frac{\mu_{TG}-\mu_{CG}}{\sqrt{\frac{(n_{TG}-1)(s_{TG})^2+(n_{CG}-1)(s_{CG})^2}{n_{TG}+n_{CG}-2}}}$	$\frac{n_{TG}+n_{CG}}{n_{TG}n_{CG}}+\frac{SMD^2}{2(n_{TG}+n_{CG})}$
Where: μ_{TG} = mean (treatment group); μ_{CG} = mean (control group); S_{TG} = standard deviation (treatment group); S_{CG} = standard deviation (control group); n_{TG} = enrollees (treatment group); n_{CG} = enrollees (control group)		
Odds Ratio (OR)	$\left(\frac{a}{b}\right)\Big/\left(\frac{c}{d}\right)=\left(\frac{ad}{bc}\right)$	$\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}$
Rate Ratio (RR)	$\left(\frac{a}{a+c}\right)\Big/\left(\frac{b}{b+d}\right)$	$\frac{1}{a}+\frac{1}{a+c}+\frac{1}{b}+\frac{1}{b+d}$
Where: a = number of individuals with kidney disease who crashed; b = number of individuals without kidney disease who crashed; c = number of individuals with kidney disease who did not crash; d = number of individuals without kidney disease who did not crash.		

All statistics in this ECRI Institute evidence report were calculated using comprehensive meta-analysis software.(12-14)

Synthesis of Results

This section summarizes the findings of our analyses for each of the four key questions.

Key Question 1: Are individuals with kidney disease at an increased risk for a motor vehicle crash?

Kidney disease, its comorbidities, complications, and treatments, have the potential to increase the risk of motor vehicle crash. Drivers with kidney disease are at risk for sudden incapacitation owing to the fluid, electrolyte, and mineral imbalances caused by kidney disease. They also have a higher incidence of cardiovascular or cerebrovascular events than the general population. The symptoms of kidney disease and the side effects from treatment may also impair safe operation of a motor vehicle by inducing fatigue, sleepiness, and cognitive impairment. This presents a concern for motor vehicle safety.

Previous systematic reviews have found little evidence on the safety of drivers with kidney disease. Dobbs reviewed the medical literature 1960–2000 and did not find any studies assessing the direct relationship between chronic kidney disease and motor vehicle crash; she did review medical literature on neurocognitive impairments associated with chronic kidney disease.(114) Dobbs observed that older studies were more likely to report cognitive impairment, and proposed that improved modern management of patients with kidney disease may reduce their cognitive impairment. This report revisits the literature with updated searches, and investigates additional potential causes of reduced driving safety, including pharmacotherapy and comorbid sleep disorders.

For this Key Question we thoroughly searched the medical literature to address the question of whether drivers with kidney disease are at an increased risk of crash. We approached this in three ways. First, we searched for and analyzed direct evidence pertaining to the association between kidney disease and crash (Key Question 1: Part A). Second, we examined indirect evidence to determine whether kidney disease has an impact on driving-related measures of cognitive or psychomotor function (Key Question 2: Part B). Finally, because excessive daytime sleepiness is a known risk factor for crash, we examined further indirect evidence on the association between kidney disease and sleep disorders (Key Question 1: Part C).

Key Question 1 Part A: Direct Evidence—Kidney disease and Crash

Identification of Evidence Base

To meet the aims of this section of the evidence report, we searched for trials that compared crash risk among individuals with kidney disease and otherwise comparable individuals who do not have kidney disease. Our search strategy is detailed in Appendix A. These searches identified

1,400 abstracts. Based on our retrieval criteria (Appendix B), we retrieved five full-length studies. When we examined the full-length articles, we found three did not meet inclusion criteria (Appendix C). These studies and the reason for their exclusion are in Table D-1 (Appendix D). Two publications (Ysander(115) and Ysander[116]) were found to otherwise satisfy inclusion criteria, but reported on the same group of patients. Since Ysander 1970(115) was the more recent publication, we considered it the primary publication for our purposes, to avoid double-counting any patients. The process used to develop the evidence base for Key Question 1 is shown in Figure 6. The included studies are in Table 11.

.Figure 6. Development of Evidence Base for Key Question 1 Part A-Direct Evidence

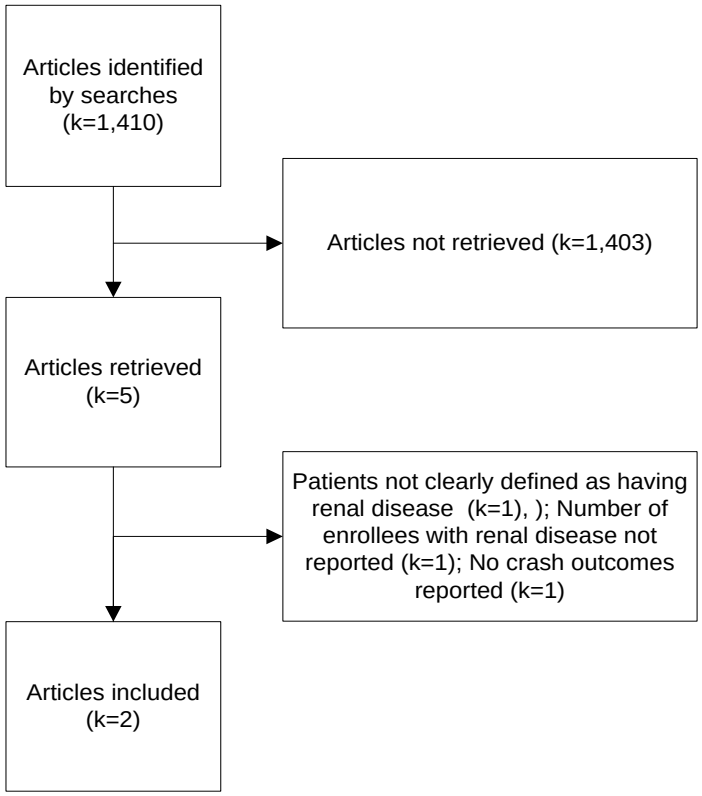


Table 11. Evidence base for Key Question 1 Part A: direct evidence

Reference	Year	Secondary Reference	Study Location	Country
McGwin et a.(51)	2000	-	Mobile County, Alabama	USA
Ysander(115)	1970	Ysander 1965(116)	Gothenburg, Bohus, and Hallan Counties	Sweden

Evidence Base

This subsection provides a brief description of the main attributes of the two studies that comprise the evidence base for Key Question 1: Part A. Here we discuss the quality of the included studies and the generalizability of each study's findings to CMV drivers. Detailed information on the design, conduct, and findings of each of the included studies is in the Study Summary Tables of Appendix G.

Characteristics of Included Studies

Two retrospective studies were identified that met the inclusion criteria for Key Question 1: Part A. The primary characteristics of these studies are in Table 12.

In both included studies, police records were assessed to determine whether individuals experienced a crash during some predefined period. While Ysander compared the incidence rate for a motor vehicle crash among patients with kidney disease to otherwise comparable healthy drivers (cohort study), McGwin compared the proportion of drivers with a renal disorder from a sample of drivers who had experienced a crash with the proportion of individuals with a renal disorder from a sample of drivers who had not experienced a crash (case-control study).

Table 12. Key Study Design Characteristics of Studies that Address Key Question 1 Part A; Direct Evidence

Reference	Year	Design (prospective/retrospective)	Comparison	Definition of Kidney disease Used	Severity of Renal Failure	Driving Exposure Controlled For?	Primary Outcome	Outcome Self-reported?
McGwin et al.(51)	2000	Retrospective case-control	Drivers who did not crash	NR	NR	No	Crash	No
Ysander(115)	1970	Retrospective cohort	Healthy drivers matched by duration of license holding, age, and gender	Nephropathy with and without hypertension and protein in urine	NR	Yes	Crash, serious driving offenses	No

*ICD: International Classification of Disease
NR: Not reported

Quality of Included Studies

Using a revised version of the Newcastle-Ottawa Quality Assessment Scale for Observational Studies we evaluated the quality (internal validity) of the two included studies (see study summary tables in Appendix G for full quality assessment). As summarized in Table 13, neither study was of high quality.

Table 13. Quality of the Studies That Assess Key Question 1 Part A: Direct Crash Evidence

Reference	Year	Quality Scale Used	Quality

McGwin et al.(51)	2000	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Low
Ysander(115)	1970	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate

Because these studies used a cohort design, they are susceptible to potential biases resulting from differences in patient characteristics, incomplete follow-up, and measurement bias (particularly in how measurements are taken and how the data are analyzed). For these reasons, cohort-control studies cannot be considered high in quality.

Both studies have the potential for measurement bias, meaning that the reports of disease state and/or risk exposure may not be accurate, potentially affecting the results of the study. Both studies were at risk for measurement bias in terms of disease state reporting. McGwin and colleagues reported on patients with self-reported "kidney disease." Self-reported outcomes are generally less reliable than data obtained from objective records. Ysander collected disease state data from drivers' license records, and reported on patients with "renal disorders." This population includes drivers with nephropathy with or without hypertension, drivers with nephropathy with proteinuria, and drivers with orthostatic proteinuria. It is possible that not all these drivers would be diagnosed as having kidney disease by current standards. Furthermore, data collected from government records do not necessarily provide reliable information on individual health status. It is known that many individuals with health disorders that will lead to restrictions on their driving license will not notify the authorities of their condition. Individuals may be reluctant to provide accurate information on their health state, or they may not understand their health state sufficiently to accurately report on it.

Both studies may also be affected by measurement bias in terms of risk exposure. Of particular import to studies that examine motor vehicle crash risk is the need to control (or match) for exposure to risk. Examples of exposure to risk in this instance include the number of miles driven per unit time, the time frame over which data were collected, and the type(s) of roads used. Ysander attempted to control for risk exposure in terms of duration of licensure, however, this metric does not capture the most important risk factor for crash—miles driven. McGwin and colleagues attempted to control for risk exposure in terms of annual distance driven. However, McGwin relied upon self-reported estimated annual mileage, which may not be precise. Even assuming that all individuals are honest, the accuracy of these data must also be viewed cautiously, because they rely on potentially inaccurate individual recollections (sometimes called "hindsight bias").

Generalizability of Evidence Base to Target Population

The purpose of this subsection is to detail the extent to which the individuals enrolled in the studies that address Key Question 1: Part A are similar to CMV drivers in the United States. Important details on the characteristics of the individuals enrolled in the studies that address Key Question 1 are in Table 14. The generalizability of the findings of the included studies to CMV drivers is unclear. As stated earlier, neither study examined crash risk specifically among individuals who held a current commercial driver's license. Exposure to risk is far lower among noncommercial vehicle drivers because noncommercial drivers drive fewer miles, on average, than CMV drivers. In addition, neither study reports on the prevalence of comorbidity, such as cardiovascular disease, which CMV drivers are likely to experience by virtue of their lifestyle. Also, women tend to be overrepresented (when compared with the number of women in the CMV driver population) in studies of crash risk among drivers with private motor vehicle driver licenses. Finally, one of the included publications studied only elderly drivers, who may be older on average than many CMV drivers.

Table 14. Generalizability of Studies That Address Key Question 1 Part A: Direct Evidence

Reference	Year	(# of individuals with kidney disease Included (n=)	Duration of kidney disease	% male	% CMV drivers	Mean age (SD) in years	Driving Exposure	% with Medically Restricted Licenses?	Generalizability to target population
McGwin et al.(51)	2000	42	NR	NR; 50.4% of total sample	NR	NR; range of total sample 65-93	NR	NR	Unclear
Ysander(115)	1970	52	NR	NR; 80% of total sample male	NR	NR; range of total sample 18-65	NR	NR	Unclear

CMV Commercial motor vehicle; NR not reported.; SD standard deviation.

Findings

The findings of the two studies (Median Quality Category = Low) that address Key Question 1: Part A are detailed in Appendix G. As noted, the evidence base for this Key Question comprises two distinct types of studies. One study compared crash risk among individuals with kidney disease and a comparable group of individuals who did not have kidney disease (a retrospective cohort design).(115) Outcome data from this study were presented as an Incident Rate Ratio (RR)[1]. The other study compared the prevalence of kidney disease among individuals who were involved in a crash and a comparable group of individuals who were not (a case-control study).

[1] The incidence of crash among individuals with kidney disease divided by the incidence of crash among comparable individuals who do not have kidney disease.

Outcome data from this study were presented as the Odds Ratio (OR)[2].(51) Although both types may be considered to address the same question from a qualitative perspective ("Does kidney disease represent an increased crash risk?"), they differ significantly from a quantitative perspective, which is why different metrics were required to assess them.

Crash Risk among drivers with kidney disease compared to drivers without kidney disease

Ysander et al. reported on the ratio of the incidence of crashes occurring among populations of individuals with kidney disease and the ratio of the incidence of crashes occurring among individuals without the disorder.(115) This study did not provide evidence to support the contention that individuals with a renal disorder are at an increased risk for a motor vehicle crash (Table 15).

Table 15. Crash Risk in Drivers With Kidney disease Compared With Drivers Without Kidney disease

Reference	Year	Units	Crash Rate Data				Evidence of Increased Crash Risk
			Crash Rate (cases)	Crash Rate (controls)	Log Rate Ratio* (95% CI)	*P* =*	
Ysander(115)	1970	Crashes per 100 drivers with or without disease	2.5	7.7	-1.13 (95% CI -2.5 to 0.28)	0.115	No

*Calculated by ECRI Institute from reported data. Effect size estimates >0.0 indicate that individuals with renal failure are at increased risk for a motor vehicle accident when compared with individuals without the disorder. Negative effect sizes show they are at decreased risk.

Prevalence of Kidney disease Among Drivers Who Did and Did Not Crash

McGwin et al. assessed the crash risk associated with kidney disease among the general driver population as an OR study.(117) Consistent with the findings of Ysander et al., the study of McGwin et al. does not provide any evidence to support the contention that individuals with a renal disorder are at an increased risk for a crash(118-120) Table 16.

Table 16. Findings of OR Study

Reference	Year	Units	Crash Rate Data				Evidence of Increased Crash Risk
			At-fault in crash	Not in crash	Log Odds Ratio* (95% CI)	*P* =*	
McGwin et a.(51)	2000	Proportion of at-fault drivers involved in crashes ind drivers not involved in crashes with kidney disease	3.2	4.7	-0.4 (95% CI -1.85 to 1.05)	0.588	No

* Calculated by ECRI Institute from reported data. Effect size estimates >0.0 indicate that individuals with kidney disease are at increased risk for a motor vehicle accident when compared with individuals without the disorder. Negative effect sizes show they are at decreased risk.

[2] The odds of an individual who crashed having kidney disease divided by the odds of an individual who did not crash having kidney disease.

Key Question 1 Part B: Indirect Evidence—Kidney disease and Neurocognitive Function

In addition to directly assessing the risk for crash, we searched for comparative trials that assessed the association between kidney disease and measures of cognitive or psychomotor function that have been linked to driving performance.

A meta-analysis exploring the relationship between neuropsychological functioning and driving ability in dementia by Reger et al.(121) categorized a series of neuropsychological tests into six cognitive domains: mental status-general cognition; attention or concentration; visuospatial skills; memory; executive function; and language. The meta-analysis concluded that driving ability tended to decline as cognitive functioning declined. The tests discussed in Reger's meta-analysis that demonstrated important relationships with on-road tests (tests actually performed in a vehicle) were in the visuospatial skills and attention or concentration cognitive domains. For non-road tests (which have the advantage of allowing more control over conditions and variables), mental status–general cognition, visuospatial skills, memory, and executive functions all demonstrated significant relationships. The meta-analysis reported several limitations in the primary studies used, including variability in participant characteristics, data reporting, driving measures, and the widely held assumption that driving tests are valid and reliable for indicating driving ability. Of special importance to this section is the acknowledgment of the wide variety of cognitive tests used in the studies included in the meta-analysis. Since many of the tests examine multiple cognitive domains and may test different aspects of each domain, assembling them into broader categories may reduce only a small part of the variability inherent in an effort to group somewhat different articles into a single, defined entity. Also, the drivers studied in Reger's analysis had dementia, so the findings may not be generalizable to drivers without dementia. Nevertheless, Reger's analysis suggests that neurocognitive tests have some meaning when considering suitability to drive.

Search Strategy

Our search strategy to identify studies on the relationship between kidney disease and neurocognitive impairment is detailed in Appendix A. These searches identified 70 potentially relevant abstracts. Based on our retrieval criteria (Appendix B), we retrieved 15 full-length articles. Examining the full-length articles, we found that seven studies did not meet inclusion criteria (Appendix C). The seven excluded studies and the reason for their exclusion are listed in Table D-1 of Appendix D. The remaining eight studies were included in the assessment. The process used to develop the evidence base for Key Question 1 is shown in Figure 6 included studies are listed in Table 17.

Figure 7. Development of Evidence Base for Key Question 2 Part B: Neurocognitive Evidence

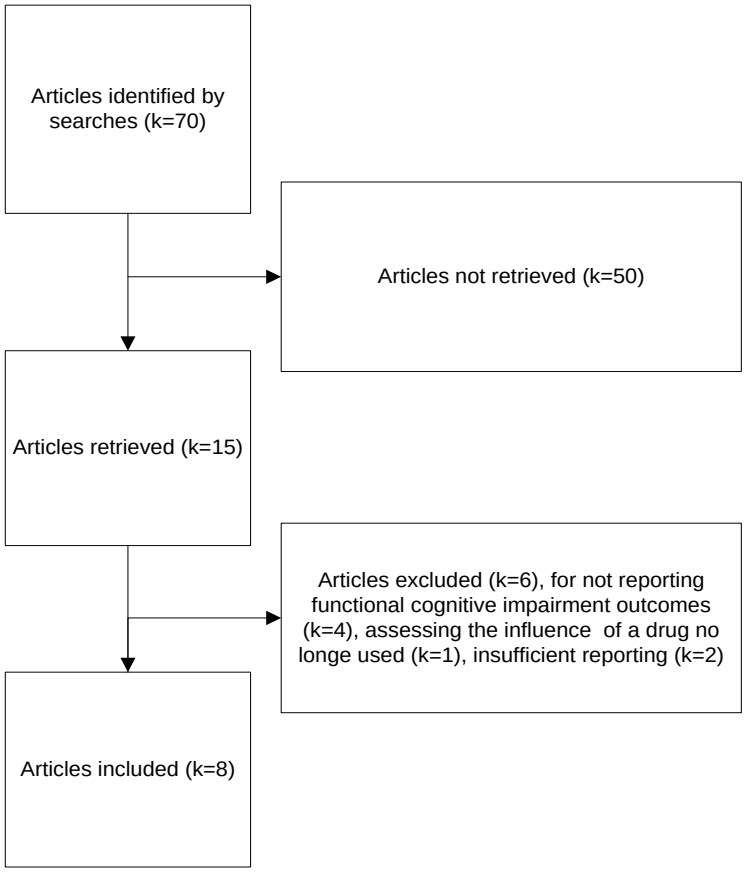


Table 17. Evidence Base for Key Question 1 Part B: Neurocognitive Evidence

Reference	Year	Study Location	Country
Pereira et al.(122)	2007	Boston, MA	USA
Thornton et al.(123)	2007	Vancouver	Canada
Murray et al.(124)	2006	St. Paul, MN	USA
Evans et al.(125)	2004	Indiana	USA
Umans and Pliskin(126)	1998	Chicago, IL	USA
Kramer et al.(127)	1996	Not reported	Austria
Pliskin et al.(128)	1996	Chicago, IL	USA
Hart et al.(113)	1983	Oklahoma	USA

Evidence Base

This subsection provides a brief description of the main attributes of the studies that make up the evidence base for Key Question 1: Part B: indirect evidence. Here we discuss information on the quality of the included studies, and the generalizability of each study's findings to CMV drivers of .

Characteristics of Included Studies

The primary characteristics of the eight included studies that address Key Question 1: Part B-indirect evidence is presented in Table 18. All patients enrolled in these studies had severe kidney disease. All studies are prospective cohort studies that compared the neurocognitive function of people with kidney disease with the neurocognitive function of people without kidney disease (most frequently healthy controls).

Participants in cohort studies are not randomized or otherwise prospectively allocated to their treatment (or no-treatment) group, therefore, this type of study is more susceptible to potential bias than randomized controlled trials (RCTs). In these studies, the mean results from patients with kidney disease were compared with the mean results from people without kidney disease. Two of the studies used normative data as the basis for comparison.(122,125) In this evidence report, we label these studies as historically controlled cohort studies. Four compared the cognitive function of people with kidney disease with that of matched healthy controls(123,124,126,127), and two compared the cognitive function of people with kidney disease with that of matched controls with other chronic illnesses.(113,128)

Table 18. Key Study Design Characteristics of Studies That Address Key Question 1 Part B: Neurocognitive Evidence

Reference	Year	Severity of Kidney disease	Severity Level Definition	Prospective or Retrospective	Study Design Type	Comparison
Pereira et al 2007(122)	2007	Severe	Requiring hemodialysis	Prospective	Historically controlled cohort	Normative data
Thornton et al.(123)	2007	Severe	Requiring hemodialysis	Prospective	Cohort controlled	Age- and education-matched healthy controls
Murray et al.(124)	2006	Severe	Dialysis patients	Prospective	Cohort controlled	Age-matched controls
Evans et al.(125)	2004	Severe	Requiring hemodialysis	Prospective	Historically controlled cohort	Normative data
Umans and Pliskin(126)	1998	Severe	Requiring hemodialysis	Prospective	Cohort controlled	Age- and education-matched controls with normal renal function
Kramer et al.(127)	1996	Severe	Requiring hemodialysis; patients subsequently underwent transplantation	Prospective	Cohort controlled	Gender- and age-matched healthy controls
Pliskin et al.(128)	1996	Severe	Requiring hemodialysis	Prospective	Cohort controlled	Age- and education-matched controls with other chronic illnesses
Hart et al.(113)*	1983	Severe	On hemodialysis or uremic	Prospective	Cohort controlled	Patients with other chronic medical conditions

**Hart et al.(113) also compared scores of dialyzed and non-dialyzed uremic patients; this outcome is assessed in Key Question 3

Quality Assessment

We assessed the quality of each of these studies using the Revised Newcastle–Ottawa Quality Assessment Scale for Cohort Studies. The findings of our assessment are summarized in Table 19. None of the studies was rated high in quality. Full quality assessment responses for each study are reported in Appendix F.

Table 19. Quality of the Studies That Assess Key Question 1 Part B: Neurocognitive Evidence

Reference	Year	Quality Scale Used	Quality Category
Pereira et al 2007(122)	2007	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Thornton et al.(123)	2007	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Murray et al.(124)	2006	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Evans et al.(125)	2004	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Umans and Pliskin(126)	1998	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Kramer et al.(127)	1996	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Pliskin et al.(128)	1996	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Hart et al.(113)	1983	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate

Generalizability of Evidence Base to Target Population

The purpose of this subsection is to detail the extent to which the individuals enrolled in the studies that address Key Question 1: Part B are similar to CMV drivers in the United States. Important characteristics of the individuals included in the studies that address Key Question 1: Part B are presented in Table 20. The generalizability of the findings of the studies included in this section of the report to CMV drivers is unclear. None of the included studies was specifically designed to measure the association of kidney disease with cognitive functioning in relation to driving performance. None of the studies reported on the employment status of enrolled patients (in particular whether they included CMV drivers), drivers license type, or driving exposure. Where reported, the mean age of enrolled patients was typically middle-aged; however, one study reported that most subjects enrolled were older.(124) Of the six studies that reported the gender distribution of studied patients, all reported that about half were male, over-representing females compared with the CMV driving population.

Table 20. Generalizability of Studies That Address Key Question 1 Part B: Neurocognitive Evidence

Reference	Year	(Number of Individuals with kidney disease Included (n=)	Duration of kidney disease	% Male	% CMV Drivers	Mean Age (SD) in Years	Driving Exposure	% with Medically Restricted Licenses?	Generalizability to Target Population
Pereira et al.(122)	2007	25	NR	44%	NR	58.3 (13.8)	NR	NR	Unclear
Thornton et al.(123)	2007	51	NR	NR	NR	NR (range 38-89)	NR	NR	Unclear
Murray et al.(124)	2006	101	NR: Duration of dialysis 3 (3.5) years	56.4%	NR	70.4 (9.4)	NR	NR	Unclear
Evans et al.(125)	2004	147	NR: Duration of dialysis 5 (5.1) years	NR	NR	44.4 (14.1)	NR	NR	Unclear
Umans and Pliskin(126)	1998	10	NR: Duration of dialysis range 0.5 to 10 years	NR	NR	61 (16)	NR	NR	Unclear
Kramer et al.(127)	1996	15	NR: Duration of dialysis 1.5 years (range 3 months – 8 years)	46.7%	NR	45 (13)	NR	NR	Unclear
Pliskin et al.(128)	1996	16	NR: Duration of dialysis 3.2 (range 0.6-7) years	43.7%	NR	59.8 (range 36-77)	NR	NR	Unclear
Hart et al.(113)	1983	62	NR: Duration of dialysis 2.7 (2.7) years	50%	NR	NR: Range 17-62	NR	NR	Unclear

CMV; NR not reported; SD standard deviation.

Findings

The eight included studies assessed a variety of neurocognitive domains believed to be relevant to driving. These studies may provide important information on the neurocognitive function of people with chronic kidney disease, however, they cannot be considered to be a robust substitute for actual crash risk data. While the neurocognitive tests examined in this evidence report attempt to measure performance in domains that have the potential to affect driving performance, the magnitude of the true association between these tests and crash risk is unknown. Consequently, the data examined in this sub-section provide evidence of the plausibility that individuals with kidney disease may represent a population of individuals with an increased risk for a motor vehicle crash.

We grouped the various tests into three domains: attention and concentration, visuospatial skills, and executive function. Table 21 lists the specific tests used in the identified studies to assess neurocognitive function of individuals with kidney disease.

Table 21. Evidence Base for Key Question 1 Part B: Neurocognitive Evidence

Study	Year	Attention and Concentration									Visuospatial Skills		Executive Function		
		Mini-Mental State Examination (MMSE)	Trail Making g Test A	Wechsler Digit Span	Digit Symbol Coding	Paced Auditory Serial Attention Task (PSAT)	Attention subscale, Cognistat	Digit Vigilance Test	Continuous Performance Test	Gordon Diagnostic System Vigilance Test	Block Design	Clock Drawing	Trail Making Test B	Stroop Color-Word Test / Interference Test	
Pereira et al 2007(122)	2007	✓*	✓		✓						✓				
Thornton et al.(123)	2007												✓	✓	
Murray et al.(124)	2006	✓		✓								✓		✓	
Evans et al.(125)	2004						✓								
Umans and Pliskin(126)	1998		✓	✓		✓		✓	✓	✓			✓	✓	
Kramer et al.(127)	1996	✓	✓												
Pliskin et al.(128)	1996		✓		✓	✓					✓		✓	✓	✓
Hart et al.(113)	1983		✓	✓				✓					✓		
Totals		2	5	3	2	2	1	2	1	1	2	1	4	4	1

*Although Pereira et al. reported mini mental state examination data, this data was not used in this assessment because no comparative data was reported

For each study and outcome we present test results for kidney disease patients and control data. Control data most frequently came from cohort controls, but some studies also included normative data. Most of the studies enrolled patients in the kidney disease group who were treated with hemodialysis (noted in the tables as "HD"). Some studies were small, enrolling as few as 10 patients.

For each outcome and each patient group of each study we calculated *P*-values to assess whether a statistically significant difference in test scores existed between kidney disease patients and controls. We did not combine studies reporting the same outcome in a meta-analysis because of differences in control types, patient populations, and study methods. In the following text, we present the findings from the included studies of the outcomes listed in Table 21, divided by domain.

General

Two studies, Murray et al. and Kramer et al., reported findings of the mini-mental state examination (MMSE), a general screening tool for cognitive dysfunction.(124,127) Both studies compared the scores of hemodialysis patients with scores of controls without kidney disease. Kramer et al. compared the scores of people with kidney disease with healthy controls, and Murray et al. compared them with the scores of community controls and controls selected from outpatient general practice, diabetes, and geriatric clinics. Both studies found that hemodialysis patients performed statistically significantly more poorly on the MMSE than controls. Kramer et al. also tested the same group an average of 14 months (standard deviation 5 months) after they had undergone cadaveric (n=14) or living donor (n=1) transplantation, and found that the difference between transplant recipients and controls was no longer statistically significant. These findings are shown in Table 22. The findings suggest that some individuals with chronic renal failure treated with hemodialysis experience general cognitive impairment.

Table 22. General Cognitive Function of Individuals with Kidney disease

Test	Study	Year	Kidney disease Patients			Type of Control	Control Data			SMD (95% CI)	P=	Bottom Line: Difference Between Groups?
			N=	Mean	SD		N=	Mean	SD			
MMSE*	Murray et al.(124)	2006	101 (HD)	88.6	7.1	Cohort	101	94.3	5.7	0.885 (0.596-1.174)	<0.001	Yes
	Kramer et al.(127)	1996	15 (HD)	28.5	2.0	Cohort	45	29.5	0.8	0.839 (0.227-1.433)	0.007	Yes
			15 (TRANS)	29.1	0.9	Cohort	45	29.5	0.8	0.485 (-0.016-1.075)	0.108	No

*MMSE: mini- mental state examination; HD: treated with hemodialysis; TRANS: treated by kidney transplantation

Attention and Concentration

Seven of the eight included studies assessed attention and concentration using a variety of tests. Results for each study are shown outcome-by-outcome in Table 23. Most outcomes assessed by more than one study had conflicting findings: some found statistically significant differences between kidney disease patients, while others did not.

Table 23. Attention and Concentration Function of Individuals with Kidney disease

Test	Study	Year	Kidney disease Patients			Control Data			SMD (95% CI)	P=	Bottom Line: Difference Between Groups?
			N=	Mean	SD	N=	Mean	SD			
Trail Making Test A	Pereira et al 2007(122)	2007	25 (HD)	40.5	8.3	NR	50	10	Not calculable based upon reported data	<0.001*	Yes
	Umans and Pliskin(126)	1998	10 (HD)	68.5	48.1	10	67.4	57.4	0.20 (-0.820 – 0.859)	0.963†	No
	Kramer et al.(127)	1996	15 (HD)	34	10	45	28	9	0.604 (0.052 – 1.228)	0.033	Yes
			15 (TRANS)	29	8	45	28	9	0.113 -0.465 – 0.690)	0.702	No
	Pliskin et al.(128)	1996	16 (HD)	37.3	8.7	12	36.1	7.6	0.141 (-2.39 – 0.936)	0.704	No
	Hart et al.(113)	1983	24 (HD)	31.2	10.1	20	35.3	13.1	0.348 (-0.239 – 0.436)	0.245	No
			18 (Uremic)	46.8	21.5	20	35.3	13.1	0.641 (0.001 – 1.280)	0.050	Yes
Wechsler Digit Span	Murray et al.(124)	2006	101 (HD)	14.8	3.8	101	18.3	4.2	0.871 (0.583 – 1.158)	<0.001*	Yes
	Umans and Pliskin(126)	1998	10 (HD)	10.6	4.2	10	12.3	4.1	0.392 (-0.456 – 1.241)	0.365	No
Digit Span Forward	Hart et al.(113)	1983	24 (HD)	5.8	1.0	20	5.9	1.4	0.082 (-0.501 – 0.665)	0.783	No
			18 (Uremic)	6.0	1.3	20	5.9	1.4	0.072 (-0.551 – 0.696)	0.820	No
Digit Span Backward	Hart et al.(113)	1983	24 (HD)	4.7	1.1	20	4.6	1.2	0.086 (-0.497 – 0.689)	0.773	No
			18 (Uremic)	4.1	0.8	20	4.6	1.2	0.475 (-0.158 – 1.107)	0.141	No
Digit Symbol Coding	Pereira et al 2007(122)	2007	25 (HD)	7.7	3.1	NR	10	3	Not calculable based upon reported data	<0.001*	Yes
	Pliskin et al.(128)	1996	16 (HD)	6.6	2.0	12	7.6	1.9	0.496 (0.242 – 1.234)	0.188	No
Paced Auditory Serial Attention Task (PASAT) 1	Umans and Pliskin(126)	1998	10 (HD)	24.6	6.9	10	21.2	10.7	0.362 (-0.485 – 1.209)	0.403	No
PASAT 2	Umans and Pliskin(126)	1998	10 (HD)	23.6	5.1	10	22.9	11.8	0.074 (-0.766 – 0.914)	0.863	No

PASAT 3	Umans and Pliskin(126)	1998	10 (HD)	19.5	5.2	10	21.0	8.9	0.197 (-0.645 – 1.039)	0.646	No
PASAT 4	Umans and Pliskin(126)	1998	10 (HD)	17.6	6.8	10	16.2	8.3	0.177 (-0.665 – 1.018)	0.681	No
Attention Subscale, Cognistat	Evans et al.(125)	2004	147 (HD)	7.3	1.3	NR	7.1	1.2	Not calculable based upon reported data	NS*	No
Digit Vigilance Test (DVT)	Umans and Pliskin(126)	1998	10 (HD)	10.6	4.2	10	12.3	4.1	0.392 (-0.456 – 1.241)	0.365	No
DVT—Time	Hart et al.(113)	1983	24 (HD)	203.3	38.2	20	201.0	43.6	0.055 (-0.527 – 0.638)	0.852	No
			18 (Uremic)	270.2	99.9	20	201.0	43.6	0.896 (0.241 – 1.551)	0.044	Yes
DVT—Error	Hart et al.(113)	1983	24 (HD)	3.6	3.3	20	2.8	3.4	0.235 (-0.350 – 0.820)	0.431	No
			18 (Uremic)	8.2	11.1	20	2.8	3.4	0.659 (0.019 – 1.300)	0.044	Yes
Continuous Performance Test (CPT)—Hits	Umans and Pliskin(126)	1998	10 (HD)	308	22	10	320	6.0	0.713 (-0.155 – 1.581)	0.108	No
CPT—Omissions	Umans and Pliskin(126)	1998	10 (HD)	15.8	22	10	3.6	6.0	0.725 (-0.144 – 1.157)	0.102	No
CPT—Commissions	Umans and Pliskin(126)	1998	10 (HD)	5.3	4.5	10	6.6	3.4	0.312 (0.533 – 1.157)	0.469	No
CPT — Reaction time (msec)	Umans and Pliskin(126)	1998	10 (HD)	540	74	10	474	93	0.752 (-0.119 – 1.623)	0.091	No
Gordon Diagnostic System Vigilance Test (GDS)—Hits	Umans and Pliskin(126)	1998	10 (HD)	27.6	3.4	10	26.1	7.3	0.252 (-0.591-1.095)	0.558	No
GDS,Omissions	Umans and Pliskin(126)	1998	10 (HD)	2.4	3.4	10	3.9	7.3	0.252 (-0.591 – 1.095)	0.558	No
GDS, Commissions	Umans and Pliskin(126)	1998	10 (HD)	3.4	5.0	10	1.9	4.9	0.290 (-0.554 – 1.135)	0.500	No
GDS, Reaction Time (msec)	Umans and Pliskin(126)	1998	10 (HD)	46.9	13.3	10	47.9	13.1	0.073 (-0.767 – 0.912)	0.866	No

*Calculated by study authors

†All other P-values calculated by ECRI Institute

HD: treated with hemodialysis

Trans: treated by kidney transplantation

Trail Making Test A: Five included studies used the Trail Making Test A.(113,122,126-128) The five studies enrolled a total of 90 hemodialysis patients. In three studies, the hemodialysis patients performed comparably when compared with controls; in two, the hemodialysis patients' performance was worse, with results reaching statistical significance. Both studies that found statistically significant impairments compared the data from kidney disease patients to a

historically controlled cohort (normative data)(122) or gender- and age-matched healthy controls.(129) Studies where no significant difference was found used controls that were age and gender matched from other medical clinics(126), age- and education-matched controls with other chronic illnesses(128), and a cohort of patients with other medical conditions.(113) The inconsistent findings may be caused in part by differences in study design.

In the study that reported statistically significantly poorer scores among people with chronic kidney disease compared with healthy controls, the 15 ESRD patients later underwent kidney transplantation.(127) Following transplantation, their scores were no different than the controls.

One study also enrolled 18 non-dialyzed uremic patients.(113) These patients performed statistically significantly more poorly on the test than controls, while the hemodialysis patients in the same study did not, suggesting that ESRD patients without renal replacement therapy fare worse than dialyzed counterparts in cognitive impairment.

Digit Span Tests: Two studies administered the Wechsler Digit Span test to a total of 111 hemodialysis patients and an equal number of controls. Murray et al. found that, compared with controls with normal renal function, hemodialysis patients performed poorly(124), while Umans and Pliskin did not.(126) A third study, Hart et al., administered the Digit Span Forward and Digit Span Backward tests to 24 hemodialysis patients and 18 non-dialyzed uremic patients.(113) There were no significantly different findings for either group on either test compared with cohort controls.(113) Because of these conflicting findings and the small size and overall low quality of the evidence base, no conclusions can be drawn from these studies.

Digit Symbol Coding: Two studies with a total of 41 patients on hemodialysis tested digit symbol coding. Pereira et al. compared the scores of hemodialysis patients with historical controls (normative data) and found a significant impairment among hemodialysis patients(122), while Pliskin et al. compared hemodialysis patients to controls with other chronic diseases and did not find a significant difference.(128) It is unclear why the findings from these studies differ, but study designs and the controls used may play a role. Because of the small size and overall low quality of the evidence base, no evidence-based conclusions can be drawn for this outcome.

Paced Auditory Serial Attention Task (PASAT): Two studies reported this outcome, Pliskin et al. and Umans and Pliskin, on a total of 26 patients with kidney disease. Neither found a statistically significant difference between people with and without kidney disease. Umans and Pliskin compared the scores of 10 dialyzed patients with those of 10 controls and did not find a significant difference on any of the four subscales. Pliskin et al.(128), reported z-scores only for the PASAT test, so their results are not included in the table below. They did not find a statistically significant difference between individuals with ESRD and matched controls either. Although the findings from these results are consistent, we cannot draw evidence-based

conclusions because of the low quality of the evidence base and because the small number of patients in each study may have limited the authors' ability to detect a statically significant difference.

Attention Subscale, Cognistat: One study reported attention subscale findings from the CogniStat test.(125) The scores of 147 hemodialysis patients were compared with historical controls (normative data), and were not found to be significantly different.

Digit Vigilance Test: Two studies, Umans and Pliskin and Hart et al., assessed digit vigilance test scores in people with kidney disease and compared them with control subjects' scores. In both studies, a total of 34 hemodialysis patients were assessed: their scores were not found to be significantly different from the scores of controls with normal renal function(126) or the scores of a chronic illness control cohort.(113) The consistent data from these two studies suggest that hemodialysis patients do not demonstrate impairment on this test (Strength of Evidence: Acceptable). The low quality and small size of the evidence base substantially weaken the strength of this conclusion.

Hart et al. also compared the scores of 18 uremic non-dialyzed patients to cohort control scores, and found that the individuals with uremia performed significantly more poorly on both time and error subtests than the controls with other chronic illnesses.(113) However, a single, small, low-quality study cannot be used to draw evidence-based conclusions.

Continuous Performance Test: Umans and Pliskin assessed the performance of 10 hemodialysis patients compared with 10 control patients with normal renal function on the continuous performance test, including hits, omissions, commissions, and reaction time subtests, but found no significant differences.(126) However, because of the small size of this evidence base, the possibility that a statistically significant difference exists cannot be ruled out.

Gordon Diagnostic System Vigilance Test: Umans and Pliskin compared the scores of 10 hemodialysis patients with 10 controls with normal renal function on the Gordon Diagnostic System Vigilance Test, and found no significant differences on hits, omissions, commissions, or reaction times.(126) Since this evidence base is very small, the possibility that a statistically significant difference exists cannot be ruled out.

Visuospatial Skills

Visuospatial skills were assessed by a total of three studies using two different tests, as shown in Table 24, and discussed in the text below. Findings across studies were inconsistent, so it is unclear whether visuospatial skills are impaired in people with chronic kidney disease, although the possibility cannot be ruled out.

Block Design: Pereira et al. and Pliskin et al. assessed visuospatial skills and reported conflicting findings. Pereira et al. compared the scores of 25 hemodialysis patients with those of historical controls (normative data) and found a statistically significant impairment among hemodialysis patients(122), while Pliskin et al. compared the scores of 16 hemodialysis patients with those of chronic illness patients without ESRD matched for age and education and found no statistically significant difference.(128) It is possible that the different study designs contributed to the different findings. The normative data mean score was considerably higher than the mean score among controls in Pliskin et al. The larger sample size in Pereira et al. may have contributed to finding a significant effect as well.

Clock Drawing: One study assessed visuospatial skills using the clock drawing test in 101 hemodialysis patients by comparing them with the clock drawing test in a group of patients with normal renal function of the same age group (all older than 55).(124) Although the difference in the mean score was small, it was statistically significant.

Table 24. Visuospatial Skills in Individuals with Chronic Kidney disease

Test	Study	Year	Kidney disease Patients			Control Data			SMD (95% CI)	P=	Bottom Line: Difference Between Groups?
			N=	Mean	SD	N=	Mean	SD			
Block Design	Pereira et al.(122)	2007	25 (HD)	7.0	1.7	Not Reported	10	3.0	Could not be calculated based on reported data	<0.001*	Yes
	Pliskin et al.(128)	1996	16 (HD)	7.5	2.3	12	6.6	3.0	0.334 (-0.398-1.066)	0.372†	No
Clock Drawing	Murray et al.(124)	2006	101 (HD)	3.3	0.8	101	3.6	0.6	0.423 (0.145-0.701)	0.0003	Yes

HD: Treated with hemodialysis

*Calculated by study authors

†All other P-values calculated by ECRI Institute

Executive Function

Four studies tested executive function using an array of neurocognitive tests in a total of 119 patients with chronic kidney disease. Of these, 18 had uremia but were not dialyzed, 51 were managed without dialysis, and the remaining 127 were treated with hemodialysis. Hart et al. used a cohort control group(113), while the other four studies used matched healthy controls(123), controls with normal renal function(126), or controls with other chronic illnesses.(128) Some studies detected impairment among kidney disease patients, while others did not. The findings from these studies are listed in Table 25 and discussed in the text below.

Trail Making Test B: Four studies enrolling a total of 101 individuals with kidney disease treated with hemodialysis and 18 uremic individuals with kidney disease not treated with renal replacement therapy assessed executive function using the Trail Making Test B. In the patients

on hemodialysis, two studies did not find a significantly reduced score compared with controls without kidney disease(126) and controls with other chronic illnesses.(128) The other two studies, which compared kidney disease patients with healthy controls(123) and patients with other chronic conditions(113) did find significant impairment. The patients with uremia who were not treated with dialysis were found to have a statistically significantly lower score than controls.(113)

Stroop Tests: Four studies enrolling a total of 178 patients with kidney disease administered a Stroop test to those individuals and an equal number of controls.(123,124,126,128) The Stroop test was administered as the color–word interference test in three studies, and as the word and color test in two studies. With 10 patients and 10 controls, Umans and Pliskin did not find a significant difference between kidney disease patients and controls on the interference test, or word and color test.(126) Although Umans and Pliskin did not find a statistically significant difference, the small size of the study may have limited the ability to detect an effect. The remaining three studies, with a total of 168 patients, including 117 patients on hemodialysis, did detect a significant difference. From these studies, it appears that patients with kidney disease are impaired on this outcome of executive function.

Finger Tapping Tests: One study that enrolled 16 hemodialysis patients and 16 controls with other chronic illnesses assessed dominant and nondominant hand finger tapping test.(128) The investigators did not find a statistically significant difference between the groups.

Purdue Pegboard Test: One study enrolled 24 hemodialysis patients, 18 nondialyzed uremic patients, and 20 controls with other chronic diseases, and assessed their executive function using the Purdue Pegboard Test.(113) It showed significantly poorer test results for both groups of kidney disease patients.

Table 25. Executive Function in Individuals with Chronic Kidney disease

Test	Study	Year	Kidney disease Patients			Control Data			SMD (95% CI)	P=	Bottom Line: Difference Between Groups?
			N=	Mean	SD	N=	Mean	SD			
Trail making Test B – motor speed	Thornton et al.(123)	2007	51 (no renal replacement therapy)	80.39	45.43	55	61.55	33.98	0.469 (0.085-0.852)	0.017	Yes
Trail making test B	Umans and Pliskin(126)	1998	10 (HD)	313	318	10	251	252	0.207 (-0.635-1.049)	0.630	No
Trail making test B – T-score	Pliskin et al.(128)	1996	16 (HD)	35.5	6.5	12	35.0	10.9	0.056 (-0.671-0.783)	0.880	No
Trail making test B	Hart et al.(113)	1983	24 (HD)	92.8	47.4	20	81.9	22.9	0.279 (-0.306—0.865	0.050	Yes
			18 (Uremic)	146.7	74.5	20	81.9	22.9	1.340 (0.648-2.032)	<0.001	Yes
Stroop Color-Word / Interference Test	Thornton et al.(123)	2007	51 (no renal replacement therapy)	34.53	15.38	55	27.05	10.35	0.571 (0.185-0.957)	0.004	Yes
	Murray et al.(124)	2006	101 (HD)	113.9	44.6	101	72.3	25.0	1.146 (0.850-1.443)	<0.001	Yes
	Umans and Pliskin(126)	1998	10 (HD)	23.3	12.2	10	29.5	12.7	0.778 (-0.095-1.652)	0.051	No
Stroop Word	Umans and Pliskin(126)	1998	10 (HD)	63.0	12.6	10	76.1	19.0	0.541 (-0.315-1.398)	0.081	No
Stroop Color	Umans and Pliskin(126)	1998	10 (HD)	47.8	18.5	10	57.5	15.7	0.477 (-0.376-1.328)	0.273	No
Stroop Word (T-score)	Pliskin et al.(128)	1996	16 (HD)	32.2	7.3	10	38.2	5.7	0.877 (-0.005-1.760)	0.051	No
Stroop Color (T-score)	Pliskin et al.(128)	1996	16 (HD)	31.3	10.8	10	39.2	6.4	0.863 (-0.018-1.744)	0.055	No
Stroop Color-Word (T-score)	Pliskin et al.(128)	1996	16 (HD)	35.6	7.2	10	35.2	8.8	0.048 (-0.792-0.887)	0.911	No
Finger Tapping – dominant	Pliskin et al.(128)	1996	16 (HD)	37.3	8.8	12	38.6	8.1	0.148 (-0.579-0.876)	0.690	No
Finger Tapping - nondominant	Pliskin et al.(128)	1996	16 (HD)	35.9	9.7	12	36.1	9.3	0.020 (-0.706-0.747)	0.956	No
Purdue Pegboard Test	Hart et al.(113)	1983	24 (HD)	11.8	2.5	20	13.1	1.6	0.596 (0.001-1.192)	0.050	Yes
			18 (Uremic)	11.4	2.2	20	13.1	1.6	0.873 (0.219-1.526)	0.049	Yes

HD: Treated with hemodialysis

*Calculated by study authors

†All other P-values calculated by ECRI Institute

Key Question 1 Part C:Indirect Evidence—Kidney disease and Sleep

Introduction

The purpose of this section is to assess the prevalence and severity of sleep disorders in patients with any stage of kidney disease, and to associate those factors with potential increase in crash risk. As discussed in the background section, individuals with kidney disease, especially ESRD, have a high prevalence of sleep disorders—up to 25 times that of the general population. As excessive daytime sleepiness has an intuitive relationship with crash risk, and obstructive sleep apnea has been associated with increased crash among commercial and non-CMV drivers, sleep-related disorders are of particular interest in this report. Evidence on sleep-related disorders may provide important information on the function of people with chronic kidney disease. However, as was the case in the previous sections, indirect data cannot be considered to be a robust substitute for actual crash risk data. Rather ,these data provide evidence on the plausibility that individuals with kidney disease may represent a population of individuals with an increased risk for a motor vehicle crash. While the sleep tests attempt to measure domains that have the potential to affect driving, the actual relationship between these tests and crash risk is unknown.

Search Strategy

Our search strategy to identify studies on the relationship between kidney disease and sleep disorders is detailed in Appendix A. These searches identified 27 potentially relevant abstracts. Based on our retrieval criteria (Appendix B), we retrieved nine full length articles. Upon examination, we found that eight studies of those articles did not meet inclusion criteria (Appendix C). The eight excluded studies and the reason for their exclusion are listed in Table D-1 of Appendix D. The remaining study was included in the assessment. The process used to develop the evidence base for Key Question 1: Part C is shown in Figure 8. The included study is listed in Table 17.

Figure 8. Development of Evidence Base for Key Question 1 Part C: Sleep-Related Evidence

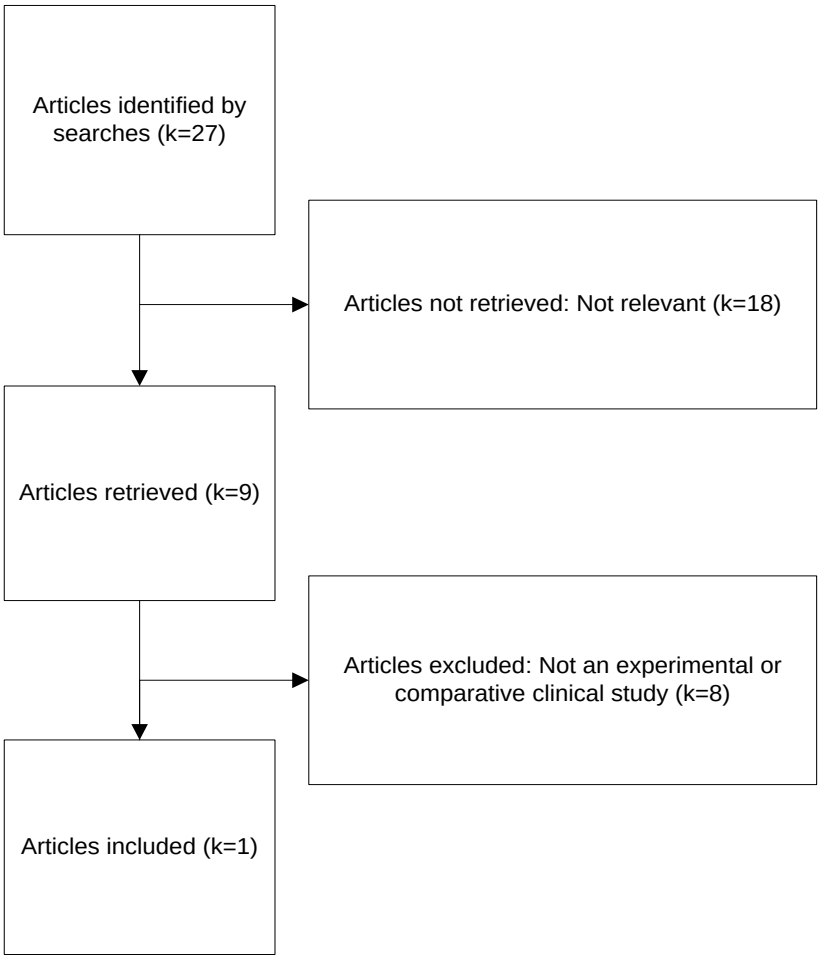


Table 26. Evidence base for Key Question 1 Part C: sleep-related evidence

Reference	Year	Study Location	Country
Unruh et al.(130)	2006	Pittsburgh, PA	USA

Evidence Base

This subsection provides a brief description of the main attributes of the single study that makes up the evidence base for Key Question 1: Part C. Here we discuss information on the quality of the included study, and its generalizability to CMV drivers.

Characteristics of Included Study

The study assessed the prevalence or severity of sleep disorders in individuals with chronic kidney disease compared with individuals without kidney disease. This prospective study compared scores of patients on hemodialysis with scores of matched community controls from the Sleep Heart Health Study.(130) The primary characteristics of the included study that addresses Key Question 1: Part C are in Table 27.

Table 27. Key Study Design Characteristics of Studies that Address Key Question 1 Part C: Sleep-Related Evidence

Study	Year	Severity of Kidney disease	Severity Level Definition	Prospective or Retrospective	Study Design Type	Comparison
Unruh et al.(130)	2006	Severe	Patients on dialysis	Prospective	Cohort-control	Participants in Sleep Heart Health Study

Quality of Included Study

We assessed the quality of the included study using the Revised Newcastle–Ottawa Quality Scale for Cohort Studies. This study was not rated as high in quality. A full quality assessment of this study is in Appendix F.

Table 28. Quality of the Studies that Assess Key Question 1 Part C: Sleep-Related Evidence

Reference	Year	Quality Scale Used	Quality Category
Unruh et al.(130)	2006	Revised Newcastle-Ottawa Quality Scale for Cohort control Studies	Moderate

Generalizability of Evidence Base to Target Population

This subsection details the extent to which the individuals enrolled in the study that addresses Key Question 1: Part C are similar to CMV drivers in the United States. The included study presents very limited demographic information to determine how comparable the enrolled individuals are to CMV drivers. Most important, the study did not state whether CMV drivers were enrolled. It did not report on the employment status of enrolled patients, drivers' license type, or driving exposure. The mean age of participants was early 60s. The proportion of men enrolled was slightly more than 70 percent; Women are somewhat overrepresented compared with the gender distribution in CMV drivers. These and other important characteristics are presented in Table 33.

Table 29. Generalizability of Studies That Address Key Question 1 Part C: Sleep-related Evidence

Reference	Year	(Number of Individuals with kidney disease Included (n=)	Duration of kidney disease	% Male	% CMV Drivers	Mean Age (SD) in Years	Driving Exposure	% with Medically Restricted Licenses?	Generalizability to Target Population
Unruh et al.(130)	2006	46	NR; median duration of dialysis 22 months	72%	NR	62.7 (NR)	NR	NR	Unclear

NR not reported.; SD standard deviation.

Findings

Because only one study met inclusion criteria for this outcome, we provide its outcomes and findings in the narrative paragraphs below.

Unruh et al. compared sleep apnea prevalence and severity in a sample of 46 hemodialysis patients with 137 participants in the Sleep Heart Health Study (SHHS).(130) The SHHS is a prospective cohort studies conducted to assess the relationship between sleep disordered breathing and cardiovascular disease. Patients with known sleep disorders *or* who were taking related treatment were excluded from this study. Controls were matched for age, gender, body mass index (BMI) and ethnicity (African American or not African American).

All patients enrolled in the study completed surveys and underwent in-home, technician-assisted partial channel polysomnography (PSG). In-laboratory PSG is the current reference standard study for diagnosing and determining the severity of obstructive sleep apnea. Among other physiological parameters such as air flow, heart rate and rhythm, and respiratory effort, PSG assesses all four of the known risk factors for crash among drivers with sleep apnea, which were identified in a previous FMCSA evidence report, "Obstructive Sleep Apnea and Commercial Motor Vehicle Driver Safety." These risk factors for crash are: BMI; severity of apnea and hypopnea (as measured using hypopnea disturbance index [HDI] or respiratory disturbance index [RDI]); presence and severity of oxygen desaturation; and presence and severity of excessive daytime sleepiness.

The differences between groups in sleep efficiency (sleep time vs. total time in bed), proportion of sleep in Stage 1 and Stage 2, and daytime sleepiness as measured by the Epworth Sleepiness Scale, were not statistically significant. However, hemodialysis patients scored statistically significantly more poorly on many other measurements, including: sleep time, proportion of patients who had rapid eye movement (REM) sleep, arousals per hour, respiratory disturbance, hypoxemic index, and lowest oxygen saturation during both REM and non-REM. Based on these

findings, Unruh and colleagues concluded their findings supported an association between hemodialysis and sleep-disordered breathing. Compared with matched controls, the odds of having severe sleep-disordered breathing was four times higher among hemodialysis patients.

Section Summary

Current direct evidence from crash studies does not demonstrate that individuals with kidney disease are at an increased risk for a crash. Indirect evidence, albeit weak, however does suggest that it is at least plausible that individuals with kidney disease may be at increased risk for a motor vehicle crash (Strength of Conclusion: Minimally Acceptable).

Direct Evidence—Crash Studies*: Our searches identified two direct crash risk studies with a total of 94 individuals with kidney disease. It is unclear how similar the drivers in these studies are to CMV drivers because few characteristics of the drivers are reported; however, it does not appear that any are CMV drivers. Driving exposure was not adequately controlled for in either study. For this and additional reasons, these studies were both rated low in quality. One study reported the crash rate of individuals with chronic kidney disease compared with community controls, and the other study reported the proportion of individuals with kidney disease that crashed compared with the proportion of drivers with kidney disease who did not crash. Neither found an increased risk of crash among drivers with kidney disease; they actually both found a reduced risk of crash. These two studies consistently suggest that noncommercial drivers with kidney disease are not at an increased risk of crash compared with drivers without kidney disease.*

Indirect Evidence—Studies of Neurocognitive Function*: Eight studies with a total of 489 patients assessed neurocognitive impairment of people with kidney disease. Overall the evidence base was of low quality. There were many differences among the studies in terms of study designs, controls selected, and outcomes reported. These eight studies reported outcomes on 18 neurocognitive measurements in four domains: general neurocognition, attention and concentration, visuospatial skill, and executive function. There was no consensus from these studies to conclude definitively that people with kidney disease have neurocognitive impairment. However, there is a sufficient quantity of evidence for multiple outcome measures with different groups of patients tested in different study designs to state that kidney disease is associated with impaired neurocognition. Therefore, the possibility that people with kidney disease are affected by neurocognitive impairment cannot be dismissed.*

Indirect Evidence—Studies of Sleep-Related Outcomes*: Only one study with 46 patients addressed this outcome. This study was of low quality and uncertain pertinence to CMV drivers. The authors found that enrolled patients with kidney disease had a prevalence of severe sleep-disordered breathing four times that of the controls from a general population, but no significant*

difference was found on other outcomes important to safe operation of a motor vehicle, including daytime sleepiness. However, previous systematic reviews have associated sleep-disordered breathing with an actual increase in motor vehicle crash. Therefore, this evidence suggests that people with kidney disease are at a greater risk of motor vehicle crash than people without.

Key Question 2: Are Medications Used to Treat Individuals with Kidney disease Associated with Increased Crash Risk Among Pre-Dialysis Patients?

Pharmacotherapy for individuals with kidney disease can help manage the underlying cause of the condition, slow the progression of renal damage, ameliorate symptoms, and treat comorbidity. Although drugs may improve quality of life and increase lifespan, adverse events and side effects may occur. Common drug side effects include sedation and psychomotor impairment. These side effects may compromise the safe operation of a motor vehicle.

According to Kay (*Measuring Impairment: Validated Test Methods for Assessing Sedating Medication*s, 2001),(131) sedation is "depression of brain functioning by a medication, manifested by" the following:

- Sleepiness, drowsiness, or fatigue
- Slowed brain activity
- Reduced wakefulness
- Impaired performance

Using this definition of sedation, one can logically conclude that an investigation of the cognitive (e.g., slowed brain activity) and psychomotor (e.g., impaired performance) effects of medications on the central nervous system could be considered an attempt to document the sedative effects of drugs.

Specific performance measures that evaluate the sedative effects of medications include simulation, cognitive testing, and psychomotor testing. Critical cognitive domains for demonstrating sedation include the following:

- Vigilance: The capacity to sustain attention under conditions of minimal arousal. These tests "appear to be the most sensitive measures for detecting the sedation effects that may contribute to accidents."(131)
- Divided attention: The ability to perform simultaneous mental activities (also referred to as 'dual tasking').
- Working memory: The ability to hold information temporarily in the brain to use it in a calculation or other mental activity.

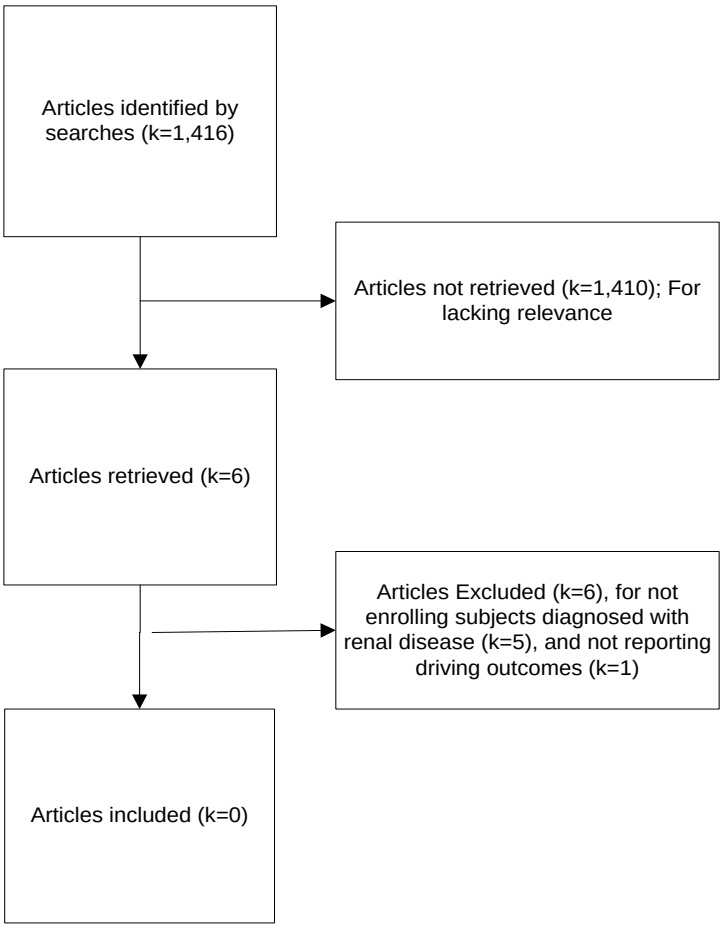
Some medications commonly administered to people with kidney disease have been associated with impaired driving in other populations. Antihistamines, taken for pruritis symptoms by patient with ESRD, have been associated with impaired driving. Diphenhydramine (Benadryl) has been found to impair measures of driving ability, such as braking time and consistent following distance, in healthy test subjects during experimental road tests.(98-100) The anticoagulant Warfarin, which people with kidney disease may take daily to prevent a cardiovascular or cerebrovascular event or use during dialysis to prevent blood clots, was studied in a general population of elderly drivers in Canada: it was not associated with an increased rate of crash.(101) However, anticoagulants were associated with an increased risk of at-fault crash involvement among elderly drivers in another assessment of driving records.(102) The same study also found angiotensin converting enzyme (ACE) inhibitors to be associated with an increased risk of at-fault crash, but not calcium channel blockers or vasodilators, which are also used to treat hypertension. The effects of these drugs in people with chronic kidney disease may be different. In addition, people with chronic kidney disease have comorbidity and usually undergo polypharmacy, and may therefore experience different reactions to the drugs than a general population.

In Key Question 2, we assess the association between medications for kidney disease and motor vehicle crash three ways. First, we attempt to directly associate medications and actual crash in drivers with kidney disease who are taking medications. Second, we indirectly associate crash risk with medications in people with kidney disease through assessment of neurocognitive status. Third, we indirectly assess the association of medications on crash by assessing sleep-related outcomes, such as excessive daytime sleepiness.

Key Question 2 Part A: Direct Evidence—Kidney disease Medications and Crash

Using criteria described in Appendix A, we searched the medical literature for studies assessing the risk of crash among drivers using drugs administered to people with chronic kidney disease. Our searches identified 1,416 potentially relevant abstracts. Based on the retrieval criteria in Appendix B, we retrieved six of them. Upon full evaluation, none was found to meet the inclusion criteria, shown in Appendix C. Reasons for each study's exclusion are listed in Appendix D, Table D-2. The development process of this evidence base is shown in Figure 9 below. As we did not identify any relevant studies, we were prevented from addressing the relationship between medications and crash.

Figure 9. Development of Evidence Base for Key Question 2: Direct Evidence

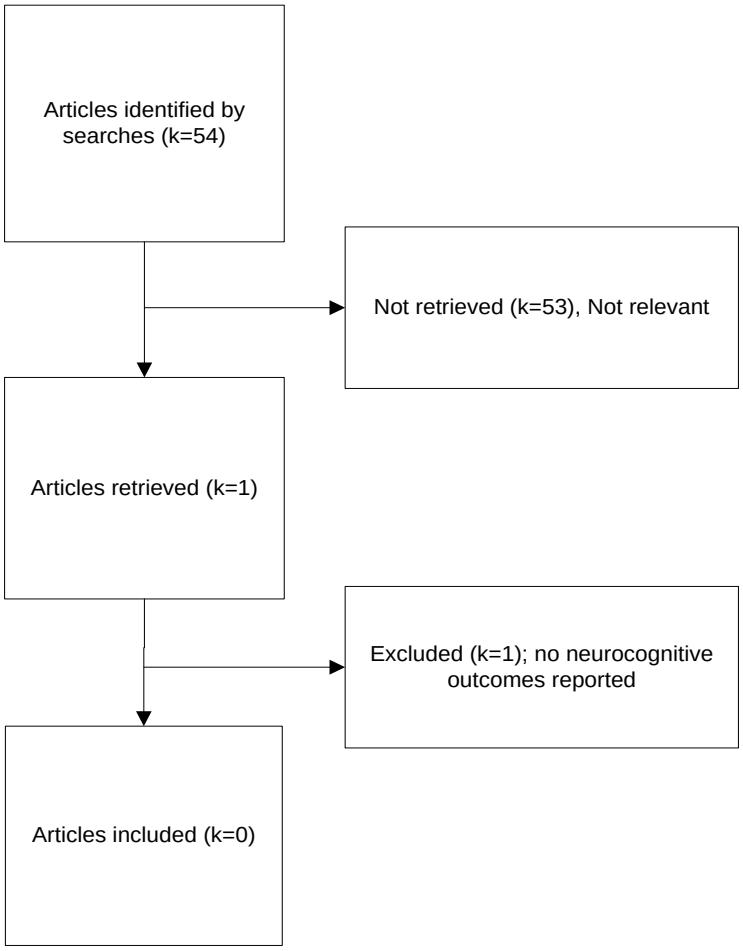


Key Question 2 Part B: Indirect Evidence—Medications for Kidney disease and Neurocognitive Function

In the first part of this key question, we considered data associating use of certain medications and crash. To further investigate the effects of medications commonly taken by people with kidney disease on driving, we searched for information on their neurocognitive effects. The purpose of this section of Key Question 2 is to assess whether neurocognitive function that can affect driving ability is compromised by medication taken by people with kidney disease not requiring renal replacement therapy. The neurocognitive effects of medication taken with renal replacement therapy are assessed in Key Question 3 for dialysis and Key Question 4 for transplant recipients.

Our searches (strategies shown in Appendix A), identified 54 potentially relevant articles. Using the criteria in Appendix B, we retrieved one that appeared relevant. The other abstracts were either not relevant or pertained to dialysis patients (addressed in Key Question 3). Upon full examination of the retrieved study, we found it was not relevant to the outcome of interest. The citation and reason for exclusion is shown in Appendix D, Table D-2. The development of the evidence base for this Key Question is shown in Figure 10, below. The absence of relevant studies prevented us from assessing the neurocognitive effects of medications in pre-dialysis kidney disease patients.

Figure 10. Development of Evidence Base for Key Question 2 Part B: Neurocognitive Evidence



Key Question 2 Part C: Indirect Evidence—Medications for Kidney disease and Sleep

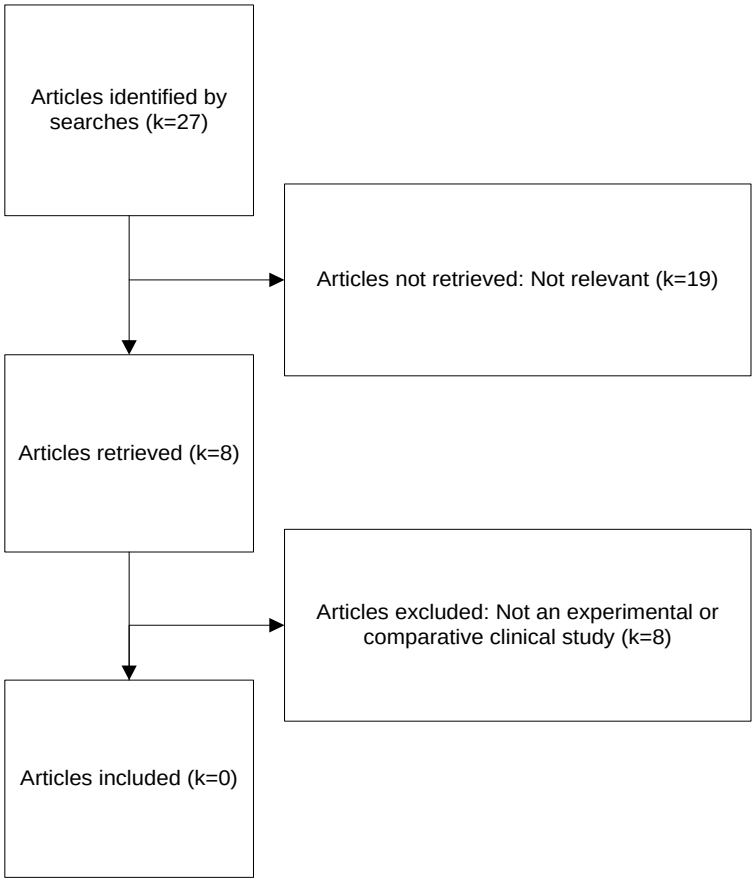
The purpose of this section is to assess the relationship between kidney disease and medications, and to associate those factors with potential increase in crash risk. As discussed in the background section, a variety of medications are used to treat symptoms of kidney disease and its underlying causes. Some of these medications may affect sleep. Medications can affect sleep by inducing drowsiness during the day or relaxing the upper airway enough to cause sleep apnea during sleep. As noted above, disturbed sleep and daytime sleepiness are associated with an increased risk for a motor vehicle crash.

Search Strategy

Our search strategy to identify studies on the relationship between kidney disease and sleep disorders is detailed in Appendix A. These searches identified 27 potentially relevant abstracts. Based on our retrieval criteria (Appendix B), we retrieved eight in full length. Upon examination

of the full-length articles, we found none of the studies met our inclusion criteria (Appendix C). The eight excluded studies and the reason for their exclusion are listed in Appendix D, Table D-2. The process used to develop the evidence base for Key Question 2: Sleep-related Evidence is shown in Table 11. As no relevant studies were identified, no assessment is possible for this outcome.

Figure 11. Development of Evidence Base for Key Question 2 Part C: Sleep-Related Evidence



Section Summary

No conclusions regarding the effect of medications on crash risk in pre-dialysis kidney disease patients can be drawn at the present time.

Our searches, including both electronic and hand searches, did not identify any studies that assessed the association of medications in pre-dialysis kidney disease patients on direct or indirect crash risk.

Key Question 3: Are Dialysis and Accompanying Drug Treatments Associated with an Increase in Motor Vehicle Crash Risk?

There is concern that people with ESRD treated with dialysis and related drugs may be at a particularly increased risk of crash. ESRD patients may be at particular risk of impaired driving ability because of the more severe hypertension and anemia that generally accompanies ESRD. Because dialysis can only provide partial renal replacement function (about 10 percent), and because of the intermittent nature of the treatment (especially hemodialysis), patients may experience fluctuations in symptoms. Fluctuations in body fluid composition could contribute to hypertension and related cognitive impairment and increase the risk of a cardiovascular or cerebrovascular event.

To address the issue of whether people treated with dialysis are at an increased risk of crash, we sought three types of data. First, we sought direct evidence. Ideally, crash data would be available that compared crash risk among individuals with ESRD who were either receiving or not receiving dialysis (Part A). Because most people with ESRD will be treated with dialysis, such studies are very unlikely to exist. Second, we sought data from studies that examined the potential impact of dialysis on driving-related cognitive and psychomotor function (Part B). Third, we searched for evidence on the impact of dialysis on sleep patterns (Part C).

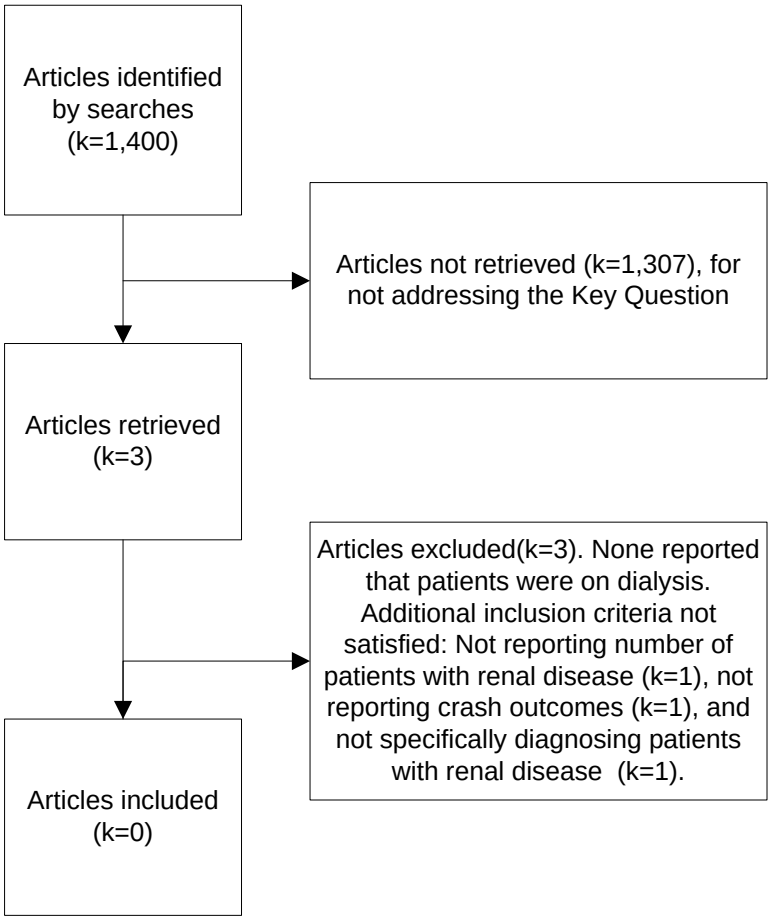
When addressing this key question, we paid particular attention to whether type of dialysis (hemodialysis or peritoneal dialysis) or types of medications were influential. In addition, we considered the importance of the effect of time, including time between dialysis sessions, and whether impairment changed over time.

Key Question 3: Part A: Direct Evidence—Dialysis and Crash Risk

Identification of Evidence Base

A total of 1,400 potentially relevant articles were identified through our literature searches (see Appendix A for our search strategy). Based on reading their abstracts, we retrieved three that appeared to be relevant (see Appendix B for retrieval criteria). However, upon closer examination, we found that none met our inclusion criteria (see Appendix C). Therefore, we did not identify any articles that directly assess the relationship between dialysis and crash. Figure 12 is a diagram of the process of exclusion. The absence of evidence precludes us from attempting to draw any conclusions regarding dialysis and accompanying treatments and crash risk.

Figure 12. Development of Evidence Base for Key Question 3 Part A: Direct Evidence



Key Question 3 Part B: Indirect Evidence—Dialysis and Neurocognitive Function

Identification of Evidence Base

Although we have chosen to examine data from instruments that measure aspects of cognitive and psychomotor that are thought to be associated with driving performance, the precise characteristics of these relationships are not well understood. Consequently, one cannot confidently infer that an observed deficit in any of these measures is indicative of an increased crash risk. However, one can infer that it is at least plausible that an individual with such a deficit is a higher crash risk than an individual who does not have the deficit.

Our searches (see Appendix A for strategy) identified 54 relevant studies. Based on our retrieval criteria (Appendix B), we retrieved 25 full studies. Upon full assessment, we excluded 12 of the retrieved studies from the evidence base. Reasons for exclusion included not reporting neurocognitive impairment outcomes (k=4), insufficient reporting (k=3), enrollment of fewer than 10 patients per arm (k=2), inadequate control (k=1), and administering an outdated

treatment (k=1) patients not treated with dialysis (k=1). These studies are listed in Appendix D, Table D-3. The process of developing this evidence base is shown in Figure 13, below. The 13 studies that met our inclusion criteria are listed in Table 30.

We have subdivided the evidence base by comparison:

- Compared with other individuals with ESRD not on dialysis
- Compared with people without kidney disease
- Comparing outcomes for the same group and different time points (e.g., before and after dialysis session)
- Comparing dialysis types
- Pertaining to drugs

One of the included studies(132) addressed two comparisons.

Figure 13. Development of Evidence Base for Key Question 3 Part B: Neurocognitive Evidence

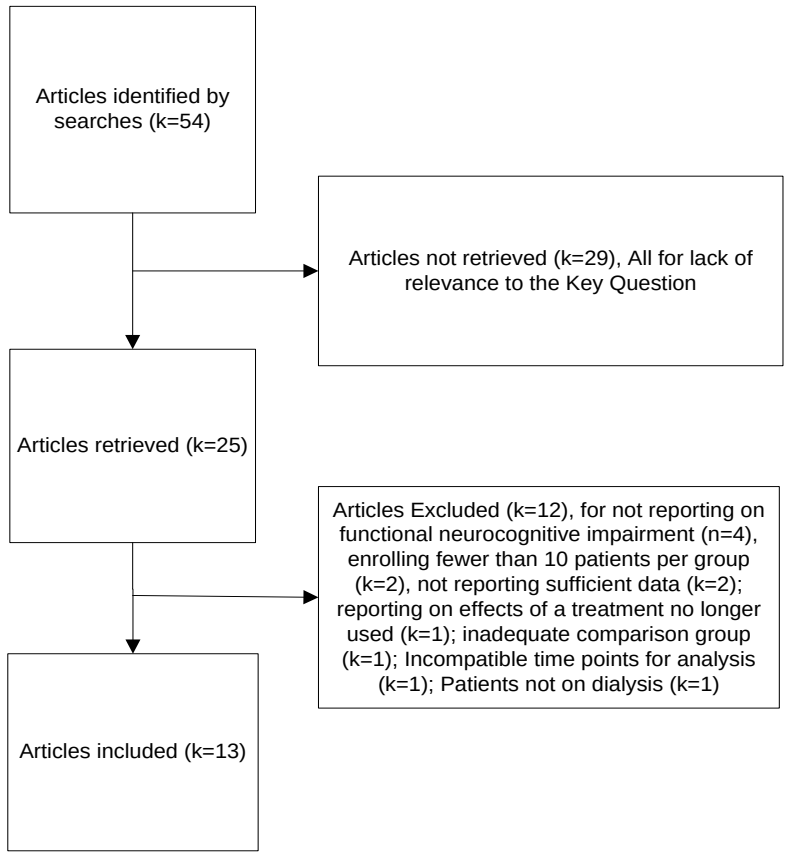


Table 30. Evidence Base for Key Question 3 Part B: Neurocognitive Evidence

Reference	Year	Study Location	Country
Compared to Other Individuals with ESRD not on Dialysis			
Hart et al.(113)	1983	Oklahoma	USA
Compared to People without Kidney disease			
Pereira et al 2007(122)	2007	Boston, MA	USA
Murray et al.(124)	2006	St. Paul, MN	USA
Evans et al.(125)	2004	Indiana	USA
Umans and Pliskin(126)	1998	Chicago, IL	USA
Pliskin et al(52)	1996	Chicago, IL	USA
Comparing Time Points			
Murray et al.(133)	2007	Minneapolis and St. Paul, MN	USA
Griva et al.(134)	2003	Not reported	UK
Williams et al.(135)	2004	Upstate New York	USA
Ratner et al.(136)	1983	Detroit, MI	USA
Comparing Dialysis Types			
Griva et al.(134)	2003	Not reported	UK
Buoncristiani et al.(137)	1992	Not reported	Italy
Drugs			
Altmann et al.(138)	2007	Not reported	NR
Marsh et al.(126)	1991	Los Angeles, CA	USA

Evidence Base

This section briefly describes the main attributes of the 13 studies that comprise the evidence base for Key Question 3: Neurocognitive Evidence. We discuss the quality of the included studies, and the generalizability of their findings to drivers of CMVs.

Characteristics of Included Studies

All 13 included studies prospectively enrolled patients with ESRD receiving dialysis with the specific aim of assessing their neurocognitive function. In 10 of the studies, all patients were treated with hemodialysis. In 2 of the studies, patients were treated with either hemodialysis or peritoneal dialysis.(132,137) One study enrolled a group of patients on hemodialysis and a group of uremic patients with ESRD who were not being treated with renal replacement therapy.(113)

The designs of the studies included in the evidence base for Key Question 3: Part B varied widely and included the following: Historically controlled cohort studies (which all used normative data as the basis of comparison) (k=3), a contemporaneous cohort study (k=5), observational pre-post (k=2) or time-series studies (k=3), and a single randomized controlled arm trial (k=1). These numbers add up to 14 because one of the publications conducted more than one study type and made more than one comparison. Griva et al. compared data from

hemodialysis patients with that of a cohort of peritoneal dialysis patients, and considered the treatment group data as time series as well.(139)

The differences in study designs cause differences in the studies that make their findings difficult to compare, and may make their combination in meta-analysis inappropriate. Differences in study designs are not limited to study types, including cohort-control, pre-post, and cohort study designs. Within the cohort–control studies, design varied. Hart et al. and Pliskin et al. conducted cohort–control studies and compared the scores of hemodialysis patients with other patients with chronic medical conditions(113,128), while Murray et al. compared the scores with those of healthy controls.(126) Buoncristiani et al. published a cohort study comparing the scores of hemodialysis and peritoneal dialysis patients.(137) Among the pre–post and time–series studies, researchers selected different time points at which to administer tests. To promote comparability, we limited our analysis to the difference in scores within two hours before dialysis and 20 to 30 hours after dialysis. Three of the four cohort studies compared the scores of dialysis patients with normative data.(122,124,125) This type of study design fails to control for confounding factors, such as age.

The key study design characteristics of all included studies that report data on the neurocognitive function of dialysis patients are shown in Table 31, below.

Table 31. Key Study Design Characteristics of Studies That Address Key Question 3 Part B: Neurocognitive Evidence

Reference	Year	Severity of Kidney disease	Severity Level Definition	Prospective or Retrospective	Study Design Type	Comparison
Compared to Other Individuals with ESRD not on Dialysis						
Hart et al.(113)	1983	Severe	On hemodialysis or uremic	Prospective	Cohort control	Patients with other chronic medical conditions
Compared to Individuals without Kidney disease						
Pereira et al 2007(122)	2007	Severe	Requiring hemodialysis	Prospective	Historically controlled cohort	Normative data
Murray et al.(124)	2006	Severe	Hemodialysis patients who would later receive kidney transplant	Prospective	Historically controlled cohort	Normative data
Evans et al.(125)	2004	Severe	Requiring hemodialysis	Prospective	Historically controlled cohort	Normative data
Umans and Pliskin(126)	1998	Severe	Requiring hemodialysis	Prospective	Cohort control	Age- and education-matched controls with normal renal function
Pliskin et al.(128)	1996	Severe	Requiring hemodialysis	Prospective	Cohort control	Age- and education-matched controls with other chronic illnesses
Comparing Time Points						
Murray et al.(133)	2007	Severe	Requiring hemodialysis	Prospective	Time series	Time series before, during, and the day after dialysis
Williams et al.(135)	2004	Severe	Requiring hemodialysis	Prospective	Time series	Time series based upon time after last weekly hemodialysis session
Griva et al.(132)	2003	Severe	Requiring hemodialysis	Prospective	Pre-post	Pre–post dialysis
Ratner et al.(136)	1983	Severe	Requiring hemodialysis	Prospective	Time series	Time series based on time after last weekly hemodialysis session
Comparing Dialysis Types						
Griva et al.(132)	2003	Severe	Requiring dialysis	Prospective	Cohort	Patients on hemodialysis and patients on peritoneal dialysis
Buoncristiani et al.(137)	1992	Severe	Requiring dialysis	Prospective	Cohort	Patients on hemodialysis and peritoneal dialysis who were comparable in terms of age and time on dialysis
Drugs						
Altmann et al.(138)	2007	Severe	Requiring hemodialysis	Prospective	Parallel-arm controlled trial	Other hemodialysis patients on different drugs
Marsh et al.(126)	1991	Severe	Requiring hemodialysis	Prospective	Pre-post	Scores before and after treatment

Quality Assessment

We assessed the quality of all studies included in this evidence base using several different quality assessment instruments, depending on the study design. Instruments used included the Revised Newcastle–Ottawa Quality Assessment Scale for observational studies, the ECRI Institute Quality Scale for Pre–Post Studies, and the ECRI Institute Quality Scale for Controlled Studies. For studies that assessed more than one comparison included in the analysis, we used

different instruments as appropriate. For instance, Griva et al.(132) compared neurocognitive tests scores of individuals on hemodialysis and peritoneal dialysis, and also compared the scores of the individuals with kidney disease at different time points. For the first comparison, we rated the quality using the Revised Newcastle–Ottawa Quality Assessment Scale for Cohort Studies. For the second comparison, we rated the quality using the ECRI Institute Quality Scale for Pre–Post Studies.

The findings of our assessment of the quality of the articles included in the evidence base for Key Question 3: Part B are presented in Table 32. None of the included studies was of high quality.

Table 32. Quality of the Studies That Assess Key Question 3 Part B: Neurocognitive Evidence

Reference	Year	Quality Scale Used	Quality
Compared to Other Individuals with ESRD not on Dialysis			
Hart et al.(113)	1983	Revised Newcastle–Ottawa Quality Assessment Scale for Observational Studies	Moderate
Compared to Individuals without Kidney disease			
Pereira et al 2007(122)	2007	Revised Newcastle–Ottawa Quality Assessment Scale for Observational Studies	Moderate
Murray et al.(124)	2006	Revised Newcastle–Ottawa Quality Assessment Scale for Observational Studies	Moderate
Evans et al.(125)	2004	Revised Newcastle–Ottawa Quality Assessment Scale for Observational Studies	Moderate
Umans and Pliskin(126)	1998	Revised Newcastle–Ottawa Quality Assessment Scale for Observational Studies	Moderate
Pliskin et al.(128)	1996	Revised Newcastle–Ottawa Quality Assessment Scale for Observational Studies	Moderate
Comparing Time Points			
Murray et al.(133)	2007	ECRI Institute Quality Scale for Pre–Post Studies	Moderate
Williams et al.(135)	2004	ECRI Institute Quality Scale for Pre–Post Studies	Moderate
Griva et al.(132)	2003	ECRI Institute Quality Scale for Pre–Post Studies	Moderate
Ratner et al.(136)	1983	ECRI Institute Quality Scale for Pre–Post Studies	Moderate
Comparing Dialysis Types			
Griva et al.(132)	2003	Revised Newcastle–Ottawa Quality Assessment Scale for Observational Studies	Moderate
Buoncristiani et al.(137)	1992	Revised Newcastle–Ottawa Quality Assessment Scale for Observational Studies	Low
Drugs			
Altmann et al.(138)	2007	ECRI Institute Quality Scale for Controlled Trials	Moderate
Marsh et al.(126)	1991	ECRI Institute Quality Scale for Pre–Post Studies	Low

Generalizability of Evidence Base to Target Population

The generalizability of the findings of the studies included in the evidence base for Key Question 3: Part B to CMV drivers is unclear. None of the 13 studies reported any information on type of licenses held by the enrolled patients, their driving exposure, or the proportion holding medically restricted licenses. Only one reported on employment rates, with 36.4 percent of hemodialysis patients and 35.1 percent of peritoneal dialysis patients working.(132) The percentage of males enrolled was typically about 50 percent, and ranged from 41 to 60 percent; men were underrepresented in this evidence base compared with CMV drivers. Where reported, the mean

age ranged from 46.5 to 70.4 years, but within studies generally ranged widely. No studies reported on the mean duration of kidney disease. Some reported on the duration of dialysis, which was most frequently reported as 3 to 5 years, although in some studies some patients have been treated for more than a decade. All these details are listed by study and divided by comparison made in the study, in Table 33.

Table 33. Generalizability of Studies That Address Key Question 3 Part B: Neurocognitive Evidence

Reference	Year	(Number of Individuals with kidney disease	Mean duration of kidney disease (SD)	% Male	% CMV Drivers	Mean Age (SD) in Years	Driving Exposure	% with Medically Restricted Licenses?	Generalizability to Target Population
Compared With Other Individuals With ESRD Not on Dialysis									
Hart et al.(113)	1983	62	NR: Duration of dialysis 2.7 (2.7) years	50%	NR	NR: Range 17-62	NR	NR	Unclear
Compared to Individuals without Kidney disease									
Pereira et al. 2007(122)	2007	25	NR	44%	NR	58.3 (13.8)	NR	NR	Unclear
Murray et al.(124)	2006	101	NR: Duration of dialysis 3 (3.5) years	56.4%	NR	70.4 (9.4)	NR	NR	Unclear
Evans et al.(125)	2004	147	NR: Duration of dialysis 5 (5.1) years	NR	NR	44.4 (14.1)	NR	NR	Unclear
Umans and Pliskin(126)	1998	10	NR: Duration of dialysis 0.5 to 10 years	NR	NR	61 (16)	NR	NR	Unclear
Pliskin et al.(128)	1996	16	NR: Duration of dialysis 3.2 (0.6-7) years	43.7%	NR	59.8 (range 36-77)	NR	NR	Unclear
Comparing Time Points									
Murray et al.(133)	2007	28	NR: Duration of dialysis 3.7 (2.8) years	56.4%	NR	66.7 (9.5)	NR	NR	Unclear
Williams et al.(135)	2004	20	NR. On hemodialysis 5.5 years; on CAPD** 3 years	50%	NR	49 (NR)	NR	NR	Unclear
Griva et al.(132)	2003	145	NR: Mean duration of renal replacement therapy 5.4 years	64.8%	NR	50.1 (NR)	NR	NR	Unclear
Ratner et al.(136)	1983	20	NR: Duration of dialysis mean 3.3 (1.8) years	NR	NR	46.5 (11.3)	NR	NR	Unclear
Comparing Dialysis Types									
Buoncristiani et al.(137)	1992	22	NR all on CAPD	50%	NR	60 (11)	NR	NR	Unclear

Reference	Year	(Number of Individuals with kidney disease	Mean duration of kidney disease (SD)	% Male	% CMV Drivers	Mean Age (SD) in Years	Driving Exposure	% with Medically Restricted Licenses?	Generalizability to Target Population
			>6months						
Griva et al.(132)	2003	145	NR: Mean duration of renal replacement therapy 5.4 years	64.8%	NR	50.1 (NR)	NR	NR	Unclear
Drugs									
Altmann et al.(138)	2007	360	Mean NR, Range 0.4-19.8 years	59.2%	NR	55.4 (NR)	NR	NR	Unclear
Marsh et al.(126)	1991	24	NR: Duration of dialysis mean 6.3 (5.3) years	50%	NR	46.8 (16)	NR	NR	Unclear

*CAPD: Continual ambulatory peritoneal dialysis

**One patient of unknown gender was not included in the study; this figure represents the gender distribution of the original group

Findings

The 13 included studies enrolled a total of 980 patients with kidney disease. The studies used a variety of neurocognitive tests to assess cognitive and psychomotor function of individuals treated with dialysis. As was the case above, we collected data only from measures of cognitive and psychomotor function that have a known association with driving performance. Consequently, data from 23 different neurocognitive tests were examined. As described earlier, these outcome measures were grouped into four distinct functional domains; general, attention and concentration, visuospatial skills, and executive function. The measures of cognitive or psychomotor function reported by each of the included studies are in Table 34.

Table 34. Evidence Base for Key Question 3 Part B: Neurocognitive Evidence

Study	Year	General													Visuospatial Skills				Executive Function			
		Mini-Mental State Examination (MMSE)	Trail Making g Test A	Wechsler Digit Span	Color Trails 1 and 2	Wechsler Digit Symbol Test	Symbol Digit Modalities Test	Paced Auditory Serial Attention Task (PSAT)	Attention subscale, Cognistat	Digit Vigilance Test	Continuous Performance Test	Number Connection Test	Simple Reaction Time	Choice Reaction Time	Block Design	Clock Drawing	Brief Visuospatial Memory Test (Revised)	Benton Visual Retention Test	Trail Making Test B	Stroop Color-Word Test / Interference Test	Finger Tapping	Grooved Pegboard Test
Compared to Other Individuals with ESRD																						
Hart et al.(113)	1983		✓	✓						✓									✓			
Compared to Other Individuals without Kidney disease																						
Pereira et al. 2007(122)	2007	✓	✓			✓									✓							
Murray et al.(124)	2006	✓		✓												✓			✓	✓		
Evans et al.(125)	2004								✓													
Umans and Pliskin(126)	1998		✓	✓				✓		✓	✓								✓	✓		
Pliskin et al.(128)	1996		✓			✓		✓							✓				✓	✓	✓	
Comparing Time Points																						
Murray et al.(133)	2007	✓			✓												✓					
Williams et al.(135)	2004																			✓		
Griva et al.(132)	2003		✓				✓											✓	✓			✓
Ratner et al.(136)	1983		✓																✓		✓	✓
Comparing Dialysis Types																						
Griva et al.(132)	2003		✓				✓											✓	✓			✓
Buoncristiani et al.(137)	1992	✓		✓								✓										

Study	Year	Gen-eral													Visuospatial Skills				Executive Function			
		Mini-Mental State Examination (MMSE)	Trail Making g Test A	Wechsler Digit Span	Color Trails 1 and 2	Wechsler Digit Symbol Test	Symbol Digit Modalities Test	Paced Auditory Serial Attention Task (PSAT)	Attention subscale, Cognistat	Digit Vigilance Test	Continuous Performance Test	Number Connection Test	Simple Reaction Time	Choice Reaction Time	Block Design	Clock Drawing	Brief Visuospatial Memory Test (Revised)	Benton Visual Retention Test	Trail Making Test B	Stroop Color-Word Test / Interference Test	Finger Tapping	Grooved Pegboard Test
Drugs																						
Altmann et al.(138)	2007									✓			✓	✓								
Marsh et al.(126)	1991						✓												✓			
TOTALS		4	7	4	1	2	3	2	1	3	1	1	1	1	2	1	1	2	8	4	2	3

Individuals with ESRD on Dialysis vs. Individuals Not on Dialysis

We identified and included one study that compared the cognitive and psychomotor function of 42 individuals with ESRD who were either on or not on dialysis.(113) Twenty-four enrollees received treatment with hemodialysis; the remaining 18 patients did not. The findings of this study are summarized in Table 35.

Attention and Concentration

Trail Making Test A: Patients on hemodialysis performed significantly better than patients in the non-dialyzed comparison group.

Digit Span Test: There was no significant difference in test performance on either the Digit Span –Forward test, or the Digit Span–Backward test.

Digit Vigilance Test: People treated with hemodialysis performed significantly better on both the timing and error subtests. One low-quality study provides insufficient evidence from which to draw conclusions.

Executive Function

Trail Making Test B: The group of patients treated with hemodialysis performed significantly better than the group of patients not treated with dialysis.

Table 35. Neurocognitive Function of Dialysis Patients Compared With Nondialyzed Individuals With ESRD

Domain	Test	Year	Dialysis Patients			Nondialyzed Individuals with ESRD			SMD (95% CI)	P=	Bottom Line: Difference Between Groups?
			N=	Mean	SD	N=	Mean	SD			
Attention and Concentration	Trail Making Test A	1983	24	31.2	10.1	18	46.8	21.5	0.958 (0.325–1.592)	0.003*	Yes
	Digit Span—Forward	1983	24	5.8	1.0	18	6.0	1.3	0.173 (-0.428-0.773)	0.573	No
	Digit Span—Backwards	1983	24	4.7	1.1	18	4.1	0.8	0.598 (-0.15–1.212_	0.056	No
	Digit Vigilance Test—Time	1983	24	203.3	38.2	18	270.2	99.9	0.921 (0.290–1.552)	0.004	Yes
	Digit Vigilance Test—Error	1983	24	3.6	3.3	18	8.2	11.1	0.958 (0.325–1.592)	0.059	Yes
Executive Function	Trail Making Test B	1983	24	92.8	47.4	18	146.7	74.5	0.875 (0.247–1.503)	0.006	Yes

*All p-values calculated by ECRI Institute

Comparison With Individuals Without Kidney disease

We identified and included seven studies that enrolled 412 patients with ESRD, all on dialysis. The evidence base is composed of five cohort studies and two historically controlled cohort studies. These studies administered a total of 16 neurocognitive tests with potential relevance to driving ability in four domains: general neurocognition,

attention and concentration, visuospatial skills, and executive function. The results of these tests are in Table 36.

General

Mini Mental State Examination: Two studies reported Mini Mental State Examination scores for people on hemodialysis. Murray et al. reported data on the Modified Mini Mental State Examination (3MS) scores of 338 people with ESRD on hemodialysis compared with scores of 101 people in a randomly sampled age-matched comparison group without ESRD.(124) It is not clear whether the control group was otherwise healthy or if members of the group had other chronic diseases. Pereira et al. reported on the scores of a sample of 25 patients on hemodialysis and evaluated whether they were within the "normal" range, with reference to a historically controlled cohort (normative data).

Pereira found that the mean scores and standard deviations were within the "normal" range of normative data. Murray et al. found a statistically significant difference in scores between the two groups, suggesting a general neurocognitive deficit among people on hemodialysis. Owing to the small amount of data, differences in reporting, and differences in study methods, it is unclear whether hemodialysis patients have impaired cognitive function. Therefore, we draw no conclusions for this outcome.

Attention and Concentration

Trail Making Test A: The Trail Making Test A was administered to a total of 51 hemodialysis patients in three studies.(122,126,128) Pereira et al. compared the tests scores of the hemodialysis patients with normative data.(122) The other two studies compared scores with those of controls. Pliskin et al. selected controls with other chronic diseases (osteoarthritis, rheumatoid arthritis, diabetes, and hypertension) from general medical and rheumatology clinics and matched them to hemodialysis patients by age, education, and ethnicity.(128) Umans and Pliskin also selected controls with normal renal function but other chronic diseases from medical clinics, and matched them to by age and education.(126)

Pereira et al. found a significant difference in the Trail Making Test A scores between dialysis patients and historical controls (normative data). However, the type of control they used may allow for potential confounding factors, such as age, to influence this finding. Both Pliskin et al. and Umans and Pliskin found no significant difference between patients on hemodialysis and patients with other diseases. It is unclear why the study findings differed, although study design may have played a role.

Wechsler Digit Span: Two studies with a total of 111 patients on hemodialysis used the Wechsler Digit Span test. Murray et al. compared the scores of 338 people with ESRD using hemodialysis with the scores of 101 people in a randomly sampled, age-matched comparison group without ESRD. Umans and Pliskin selected age- and education-matched controls with normal renal function who were being seen for other chronic diseases from a series of medical clinics.

Murray et al. detected a statistically significant difference between the scores of hemodialysis patients and historical controls. Umans and Pliskin did not detect a difference in scores compared with the matched controls with other ailments. It is therefore not possible to determine from this data set whether people with ESRD treated with hemodialysis perform more poorly on the Wechsler Digit Span tests, and no conclusions can be drawn. Differences in study methodology and controls selected may have played an important role in the differences in study findings.

Wechsler Digit Symbol Test: We identified two studies that administered the Wechsler Digit Symbol Test to a total of 41 patients on hemodialysis. Pereira et al. compared test scores with normative data, and Pliskin et al. compared them with controls with other chronic diseases (osteoarthritis, rheumatoid arthritis, diabetes, and hypertension) matched by age, education, and ethnicity.

Pereira et al. found a statistically significant difference in test scores compared with controls, while Pliskin et al. did not. Interestingly, the raw scores of the patients in Pereira et al. were higher than the raw scores for patients in Pliskin et al. The controls in Pliskin et al. had lower raw scores than the normative data used in Pereira et al. Given the small size of the evidence base, it is not possible to determine why these results differ, though study design may play a role.

Paced Auditory Serial Attention Task (PASAT): One study, by Umans and Pliskin, compared PASAT scores of 10 patients on hemodialysis with those of age- and education-matched controls from medical clinics. Although the controls had normal renal function, it is not clear whether they had other chronic diseases. The scores of people with kidney disease and the controls were not significantly different. The small size of the evidence base may have reduced the power to detect a statistically significant difference.

Attention Subscale—Cognistat Test: One study in the evidence base, Evans et al., compared Cognistat test scores of 147 hemodialysis patients with those of a historically controlled cohort (normative data). The findings did not show a statistically significant difference.

Digit Vigilance Test: Two studies in the evidence base reported on findings from the Digit Vigilance Test (DVT). Umans and Pliskin compared the scores of 10 hemodialysis patients with those of 10 age- and education-matched controls without kidney disease from other medical clinics. Hart et al. compared the scores of 24 hemodialysis patients to those of a cohort of 20 control subjects with normal renal function but other physical disabilities. Neither study detected a statistically significant difference in scores between people on dialysis and controls. It is unclear whether the patients on dialysis would have test scores similar to healthy controls.

Continuous Performance Test: One study, Umans and Pliskin, reported outcomes on the Continuous Performance Test (CPT). In this study, the scores of 10 hemodialysis patients were compared with the scores of 10 age- and education-matched controls. These controls did not have kidney disease but were selected from other medical clinics, so it is possible they had other diseases. There was no significant difference in the scores between groups.

Gordon Diagnostic System Digit Vigilance Test: The Gordon Diagnostic System (GDS) Digit Vigilance Test was administered in a single study. Umans and Pliskin administered the test to 10 patients on hemodialysis and 10 patients without kidney disease sampled from other medical clinics. It is unclear whether these controls had other chronic diseases. The controls were matched by age and education. The differences in test scores between groups were not statistically significant.

Visuospatial Skills

Block Design: Two studies were identified that studied performance on this test. Pereira et al. compared the tests scores of 25 hemodialysis patients with a historically controlled cohort (normative data).(122) Pliskin et al. selected controls with other chronic diseases (osteoarthritis, rheumatoid arthritis, diabetes, and hypertension) from general medical and rheumatology clinics and matched them with 10 hemodialysis patients by age, education, and ethnicity.(128)

While Pereira et al. detected a statistically significant difference between the scores of hemodialysis patients and those of the historically controlled cohort, Pliskin et al. did not detect a significant difference between the scores of hemodialysis patients and those of controls. It is unclear how hemodialysis patients would have scored compared with matched healthy controls. The studies' different findings may be at least in part caused by differences in the studies' designs.

Clock Drawing: One study, Murray et al., studied the performance of 101 hemodialysis patients on the clock drawing test compared with that of an age-matched comparison

group recruited from geriatric, general, and diabetes medical clinics. The difference in test performance between groups was statistically significant.

Executive Function

Trail Making Test B: Three studies with a total of 50 patients on hemodialysis administered the Trail Making Test B. Pliskin et al. selected age-, ethnicity-, and education-matched controls with other chronic diseases (osteoarthritis, rheumatoid arthritis, or diabetes and hypertension), Umans and Pliskin selected age- and education-matched controls from other medical clinics, and Thornton et al. selected healthy age- and education-matched controls. The cohort control group in Hart et al. was selected from patients with physical disabilities. Umans and Pliskin and Hart et al. administered the test in full, while Thornton et al. and Pliskin reported subtest scores.

Hart et al. found a statistically significant difference between the scores of hemodialysis patients and those of controls. Umans and Pliskin and Pliskin et al., however, did not. Owing to these differences, it is unclear whether patients on hemodialysis are impaired on this outcome measure. Differences may be caused by differences in study design and included patients.

Stroop Tests: Three studies that enrolled a total of 128 hemodialysis patients reported on their performance on the Stroop Color–Word Interference Test(124,126,128), and two also reported on the Stroop Color and Word tests separately.(126,128) All these studies enrolled controls with illnesses other than kidney disease. Pliskin et al. selected age-, ethnicity-, and education-matched controls with other chronic diseases (osteoarthritis, rheumatoid arthritis, or diabetes and hypertension), Umans and Pliskin selected age- and education-matched controls from other medical clinics, and Murray et al. selected controls from outpatient centers and the community.

Murray et al. detected a statistically significant difference between hemodialysis patients and controls on the word–color interference test, while Umans and Pliskin and Pliskin et al. did not. On both the color test and the word test administered separately, Pliskin et al. found a statistically significant difference, while Umans and Pliskin did not. Given these conflicting findings, it is unclear whether hemodialysis patients are affected by executive function impairment as measured by Stroop tests. Differences may be caused by differences in study design, number of included patients, and types of controls.

Finger-tapping Tests: One study reported on this test. Pliskin et al. administered the finger-tapping test to 16 hemodialysis patients and to age-, ethnicity-, and education-matched controls with other chronic diseases (osteoarthritis, rheumatoid arthritis, or

diabetes and hypertension). The studydid not detect a significant difference on either dominant or nondominant hand-tapping tests.

Purdue Pegboard Test: One study, Hart et al., reported on this test. Hart et al. administered the Purdue Pegboard test to 24 hemodialysis patients and a cohort of 20 controls who were patients with physical disabilities. A statistically significant difference between the groups was found. However, a single, small, low-quality study does not provide sufficient evidence to form evidence-based conclusions.

Table 36. Neurocognitive Function of Dialysis Patients Compared With Individuals Without Kidney disease

Domain	Test	Study	Year	Dialysis Patients			Control Data			SMD (95% CI)	P=	Bottom Line: Difference Between Groups?
				N=	Mean	SD	N=	Mean	SD			
General	Mini Mental State Examination (MMSE)	Pereira et al. 2007(122)	2007	25 (HD)	27.5	2.3	NR	Normal ≥24	NR	Not calculable based upon reported information	NA	No
	Modified Mini-Mental State Examination (3MS)	Murray et al.(124)	2006	101 (HD)	88.6	7.1	101	94.3	5.7	0.885 (0.596-1.174)	<0.001	Yes
Attention and Concentration	Trail Making Test A	Pereira et al 2007(122)	2007	25 (HD)	40.5	8.3	NR	50	10	Not calculable based upon reported information	<0.001*	Yes
		Umans and Pliskin(126)	1998	10 (HD)	68.5	48.1	10	67.4	57.4	0.20 (-0.820-0.859)	0.963†	No
		Pliskin et al.(128)	1996	16 (HD)	37.3	8.7	12	36.1	7.6	0.141 (-2.39-0.936)	0.704	No
	Wechsler Digit Span	Murray et al.(124)	2006	101 (HD)	14.8	3.8	101	18.3	4.2	0.871 (0.583-1.158)	<0.001*	Yes
		Umans and Pliskin(126)	1998	10 (HD)	10.6	4.2	10	12.3	4.1	0.392 (-0.456-1.241)	0.365	No
	Wechsler Digit Symbol Test	Pereira et al 2007(122)	2007	25 (HD)	7.7	3.1	NR	10	3	Not calculable based upon reported information	<0.001*	Yes
		Pliskin et al.(128)	1996	16 (HD)	6.6	2.0	12	7.6	1.9	0.496 (0.242-1.234)	0.188	No
	Paced Auditory Serial Attention Task (PASAT) 1**	Umans and Pliskin(126)	1998	10 (HD)	24.6	6.9	10	21.2	10.7	0.362 (-0.485-1.209)	0.403	No
	PASAT 2	Umans and Pliskin(126)	1998	10 (HD)	23.6	5.1	10	22.9	11.8	0.074 (-0.766-0.914)	0.863	No
	PASAT 3	Umans and Pliskin(126)	1998	10 (HD)	19.5	5.2	10	21.0	8.9	0.197 (-0.645-1.039)	0.646	No
	PASAT 4	Umans and Pliskin(126)	1998	10 (HD)	17.6	6.8	10	16.2	8.3	0.177 (-0.655-1.018)	0.681	No
	Attention Subscale – Cognistat	Evans et al.(125)	2004	147 (HD)	7.3	1.3	NR	7.1	1.2	Not calculable based upon reported information	NS*	No
	Digit Vigilance Test	Umans and Pliskin(126)	1998	10 (HD)	10.6	4.2	10	12.3	4.1	0.392 (-0.456-1.241)	0.365	No
	DVT - Time	Hart et al.(113)	1983	24 (HD)	203.3	38.2	20	201.0	43.6	0.055 (-0.527-0.638)	0.852	No

Domain	Test	Study	Year	Dialysis Patients			Control Data			SMD (95% CI)	P=	Bottom Line: Difference Between Groups?
				N=	Mean	SD	N=	Mean	SD			
	DVT - Error	Hart et al.(113)	1983	24 (HD)	3.6	3.3	20	2.8	3.4	0.235 (-0.350-0.820)	0.431	No
	Continuous Performance Test (CPT) – Hits	Umans and Pliskin(126)	1998	10 (HD)	308	22	10	320	6.0	0.713 (-0.155-1.581)	0.108	No
	CPT – Omissions	Umans and Pliskin(126)	1998	10 (HD)	15.8	22	10	3.6	6.0	0.725 (-0.144-1.157)	0.102	No
	CPT – Commissions	Umans and Pliskin(126)	1998	10 (HD)	5.3	4.5	10	6.6	3.4	0.312 (0.533-1.157)	0.469	No
	CPT – Reaction time (msec)	Umans and Pliskin(126)	1998	10 (HD)	540	74	10	474	93	0.752 (-0.119-1.1623)	0.091	No
	Gordon Diagnostic System Vigilance Test (GDS) - Hits	Umans and Pliskin(126)	1998	10 (HD)	27.6	3.4	10	26.1	7.3	0.252 (-0.591-1.095)	0.558	No
	GDS – Omissions	Umans and Pliskin(126)	1998	10 (HD)	2.4	3.4	10	3.9	7.3	0.252 (-0.591-1.095)	0.570	No
	GDS, Commissions	Umans and Pliskin(126)	1998	10 (HD)	3.4	5.0	10	1.9	4.9	0.290 (-0.554-1.135)	0.473	No
	GDS, Reaction Time (msec)	Umans and Pliskin(126)	1998	10 (HD)	46.9	13.3	10	47.9	13.1	0.073 (-0.767-0.912)	0.866	No
Visuospatial Skills	Block Design	Pereira et al 2007(122)	2007	25 (HD)	7.0	1.7	Not Reported	10	3	Not calculable based upon reported data	<0.001*	Yes
	Clock Drawing	Pliskin et al.(128)	1996	16 (HD)	7.5	2.3	12	6.6	3.0	0.334 (-0.398-1.066	0.372†	No
		Murray et al.(124)	2006	101 (HD)	3.3	0.8	101	3.6	0.6	0.423 (0.145-0.701)	0.0003	Yes
Executive Function	Trail Making Test B	Umans and Pliskin(126)	1998	10 (HD)	313	318	10	251	252	0.207 (-0.635-1.049)	0.630	No
		Hart et al.(113)	1983	24 (HD)	92.8	47.4	20	81.9	22.9	0.279 (-0.306-0.865)	0.050	Yes
	Trail Making Test B – T score	Pliskin et al.(128)	1996	16 (HD)	35.5	6.5	12	35.0	10.9	0.056 (-0.671-0.783)	0.880	No
	Stroop Color–Word /Interference Test	Murray et al.(124)	2006	101 (HD)	113.9	44.6	101	72.3	25.0	1.146 (0.850-1.443)	<0.001	Yes
		Umans and Pliskin(126)	1998	10 (HD)	23.3	12.2	10	29.5	12.7	0.778 (-0.095-1.652)	0.051	No
	Stroop Word	Umans and Pliskin(126)	1998	10 (HD)	63.0	12.6	10	76.1	19.0	0.541 (-0.315-1.398)	0.081	No

Domain	Test	Study	Year	Dialysis Patients			Control Data			SMD (95% CI)	P=	Bottom Line: Difference Between Groups?
				N=	Mean	SD	N=	Mean	SD			
	Stroop Color	Umans and Pliskin(126)	1998	10 (HD)	47.8	18.5	10	57.5	15.7	0.477 (-0.376-1.328)	0.273	No
	Stroop Word (T-score)	Pliskin et al.(128)	1996	16 (HD)	32.2	7.3	10	38.2	5.7	0.877 (-0.005-1.760)	0.03	Yes
	Stroop Color (T-score)	Pliskin et al.(128)	1996	16 (HD)	31.3	10.8	10	39.2	6.4	0.862 (-0.018-1.744)	0.04	Yes
	Stroop Color–Word (T-score)	Pliskin et al.(128)	1996	16 (HD)	35.6	7.2	10	35.2	8.8	0.048 (-0.792-0.887)	0.911	No
	Finger Tapping—dominant	Pliskin et al.(128)	1996	16 (HD)	37.3	8.8	12	38.6	8.1	0.148 (-1.579-0.876)	0.690	No
	Finger Tapping — nondominant	Pliskin et al.(128)	1996	16 (HD)	35.9	9.7	12	36.1	9.3	0.020 (-0.706-0.747)	0.956	No
	Purdue Pegboard Test	Hart et al.(113)	1983	24 (HD)	11.8	2.5	20	13.1	1.6	0.596 (0.001-1.192)	0.050	Yes

*P-scores calculated by ECRI Institute

**Pliskin and colleagues(128) also measured the PASAT, but reported values as z-scores. We discuss their findings in the text but did not put them in the table.

Comparing Time Points

Three studies, Murray et al., Griva et al. 2003, and Ratner et al., compared neurocognitive performance of hemodialysis patients at different time points. The purpose of these studies is to determine whether changes in neurocognitive function occur depending on time since last dialysis session. These studies examined the test results of 115 patients on hemodialysis. One study, Griva et al., also enrolled 68 peritoneal dialysis patients. All three studies compared the scores of patients before and after hemodialysis, to capture any fluctuations in neurocognitive status at different times before or since the last dialysis session. Such fluctuations could be caused by effects of ESRD that may be affected by wastes and excess fluid in the blood, such as uremia or hypertension. To investigate the possibility that continuous peritoneal dialysis patients are less susceptible to fluctuations in neurocognitive function, Griva et al. also enrolled peritoneal dialysis patients.

The three studies administered a total of 10 neurocognitive tests within the domains of general neurocognitive function, attention and concentration, visuospatial skills, and executive function. In the text below we discuss all the studies' findings on neurocognitive tests that are potentially relevant to safe operation of a motor vehicle, divided by domain. The test results and P values for each outcome are shown in Table 37.

General

Mini Mental State Examination: Murray et al. reported this outcome in a convenience sample of 18 older adults (>55 years old) treated for ESRD by hemodialysis. They compared the scores of the test administered 1 hour before hemodialysis and the day after hemodialysis. No statistically significant difference between the scores was found.

Attention and Concentration

Trail Making Test A: Two studies, Griva et al., and Ratner et al., administered the Trail Making Test A. Ratner et al. administered it to 20 adults on chronic hemodialysis, and Griva et al., administered it to 52 patient receiving hemodialysis in the hospital, 25 patients receiving hemodialysis at home, 45 patients treated with continuous ambulatory peritoneal dialysis (CAPD), and 23 patients treated with ambulatory peritoneal dialysis (APD). The results for all hemodialysis and all peritoneal dialysis patients in Griva et al. were reported together. Both studies found a significant difference in test score among hemodialysis patients, and Griva et al. also found a significant difference in peritoneal dialysis patients. The consistency between studies suggests these scores do not substantially fluctuate between treatments.

Color Trails Tests: One study reported this outcome. Murray et al., administered the Color Trails Test 1 and 2. Scores reported immediately before and the day after hemodialysis were analyzed. There was no statistically significant difference between time points. Although this suggests that hemodialysis patients are not impaired on this test with respect to time, a single study provides insufficient evidence to permit evidence-based conclusions.

Symbol Digit Modalities Tests: One study, Griva et al., administered this test to 77 hemodialysis patients and 68 peritoneal dialysis patients. The data from tests administered immediately before hemodialysis and 24 hours later was assessed. Peritoneal dialysis patients were administered the test at the same times to promote comparability. For both groups, there was a statistically significant difference in test scores. It is unclear why a difference was found for peritoneal dialysis patients.

Brief Visuospatial Memory Tests: One study, Murray et al., reported this outcome. The scores compared were those of the 25 hemodialysis patients immediately before and one day after their hemodialysis session. The differences between data were not statistically significant.

Benton Visual Retention Test: Griva et al. tested 77 hemodialysis patients and 68 peritoneal dialysis patients using the Benton Visual Retention Test. There was a

statistically significant difference in hemodialysis patients' test scores before and after hemodialysis, but there was not a significant difference in peritoneal patients' test scores taken at the same times.

Executive Function

Trail Making Test B: One study, Griva et al., administered this test to 77 hemodialysis patients and 68 peritoneal dialysis patients. There was no statistically significant difference in performance on the Trail Making Test B before and one day after hemodialysis (or concurrent, as a basis of comparison for the peritoneal dialysis patients).

Finger-Tapping Test: One study, Ratner et al., compared the performance of 20 patients with ESRD before and a day after hemodialysis treatment. No statistically significant difference in scores was found. This suggests that hemodialysis patients may not substantially fluctuate on this measure of executive function with respect to time since last hemodialysis session.

Grooved Pegboard Test: Two studies, Ratner et al. and Griva et al., administered the Grooved Pegboard Test. Scores were analyzed before hemodialysis and one day after hemodialysis. For the dominant hand, Ratner et al. detected a statistically significant difference in tests scores. However, no difference was found for the nondominant hand. Griva et al. did not find a statistically significant difference in scores for either hand.

Table 37. Neurocognitive Function of Dialysis Patients at Different Time Points

Domain	Test	Study	Year	Immediately to 2 Hours Before Dialysis			20-30 Hours After Dialysis			SMD (95% CI)	P=	Bottom Line: Difference Across Time-Points?
				N=	Mean	SD	N=	Mean	SD			
General	Mini Mental State Examination	Murray et al.(133)	2007	18 (HD)	38.9	2.16	18 (HD)	38.8	2.16	0.046 (-0.416-0.509)	0.844	No
Attention and Concentration	Trail Making Test A	Griva et al.(132)	2003	77 (HD)	53.73	37.32	77 (HD)	45.13	32.34	0.245 (0.018-0.472)	0.034	Yes
		Griva et al.(132)	2003	68 (PD)	50.49	25.98	68 (PD)	46.60	26.35	0.234 (-0.007-0.474)	0.057	No
		Ratner et al.(136)	1983	20 (HD)	53.4	18.5	20 (HD)	44.0	11.7	0.580 (0.106–1.054)	0.016	Yes
	Color Trails 1	Murray et al.(133)	2007	26 (HD)	78.7	54.5	26 (HD)	82.6	54.6	0.071 (-0.313-0.456)	0.716	No
	Color Trails 2	Murray et al.(133)	2007	26 (HD)	154.9	55.6	25 (HD)	147.3	55.0	0.137 (-0.256–0.531)	0.494	No
	Symbol Digit Modalities Test—Written	Griva et al.(132)	2003	77 (HD)	40.92	12.96	77 (HD)	47.10	15.20	0.435 (0.201–0.668)	0.001	Yes
		Griva et al.(132)		68 (PD)	41.31	12.66	68 (PD)	44.73	14.56	0.249 (0.008–0.491)	0.043	Yes
	Symbol Digit Modalities Test—Oral	Griva et al.(132)	2003	77 (HD)	45.82	14.22	77 (HD)	52.10	16.58	0.404 (0.172–0.637)	0.001	Yes
		Griva et al.(132)		68 (PD)	44.91	13.24	68 (PD)	48.61	15.87	0.251 (0.010–0.493)	0.041	Yes
Visuospatial Skills	Brief Visuospatial Memory Test (Revised)—Immediate	Murray et al.(133)	2007	25 (HD)	14.1	7.1	25 (HD)	13.8	7.0	0.043 (-0.350–0.435)	0.832	No
	Brief Visuospatial Memory Test (Revised) – Delayed	Murray et al.(133)	2007	25 (HD)	4.7	3.15	25 (HD)	5.0	3.1	0.096 (-0.297–0.489)	0.632	No
	Benton Visual Retention Test—Correct	Griva et al.(132)	2003	77 (HD)	5.08	2.30	77 (HD)	5.97	2.31	0.386 (0.155–0.618)	0.001	Yes
		Griva et al.(132)	2003	68 (PD)	4.75	1.98	68 (PD)	4.97	1.74	0.118 (-0.121-0.356)	0.334	No
	Benton	Griva et	2003	77	8.64	5.46	77	6.61	5.30	0.377	0.001	Yes

Domain	Test	Study	Year	Immediately to 2 Hours Before Dialysis			20-30 Hours After Dialysis			SMD (95% CI)	P=	Bottom Line: Difference Across Time-Points?
				N=	Mean	SD	N=	Mean	SD			
	Visual Retention Test - Errors	al.(132)		(HD)			(HD)			(0.146–0.608)		
		Griva et al.(132)	2003	68 (PD)	8.47	4.51	68 (PD)	7.82	3.85	0.154 (-0.085-0.393)	0.207	No
Executive Function	Trail Making Test B	Griva et al.(132)	2003	77 (HD)	97.92	51.72	77 (HD)	90.02	51.72	0.153 (-0.072-0.377)	0.183	No
		Griva et al.(132)	2003	68 (PD)	99.32	44.74	68 (PD)	99.964	46.74	0.014 (-0.224-0.252)	0.908	No
	Finger Tapping Test—Nondominant Hand	Ratner et al.(136)	1983	20 (HD)	41.3	7.5	20 (HD)	43.0	7.5	0.227 (-0.217–0.671)	0.317	No
	Grooved Pegboard Test—Dominant Hand	Griva et al.(132)	2003	77 (HD)	88.66	29.78	77 (HD)	85.12	28.81	0.121 (-0.103–0.345)	0.291	No
		Griva et al.(132)	2003	68 (PD)	93.65	34.28	68 (PD)	91.95	32.16	0.051 (-0.187-0.289)	0.674	No
	Grooved Pegboard Test—Nondominant Hand	Griva et al.(132)	2003	77 (HD)	100.19	34.59	77 (HD)	95.40	34.31	0.139 (-0.085–0.363)	0.225	No
		Griva et al.(132)	2003	68 (PD)	104.61	43.64	68 (PD)	103.25	39.71	0.033 (-0.205–0.270)	0.789	No
	Grooved Pegboard Test—Dominant Hand—time out	Ratner et al.(136)	1983	20 (HD)	26.3	8.8	20 (HD)	21.0	3.2	0.687 (0.200–1.174)	0.006	Yes
	Grooved Pegboard Test—Dominant Hand—time in	Ratner et al.(136)	1983	20 (HD)	85.6	20.6	20 (HD)	74.7	16.9	0.573 (0.100–1.046)	0.018	Yes

Comparing Dialysis Types

Two studies, Griva et al. 2003, and Buoncristiani et al., compared neurocognitive test scores in cohorts of ESRD patients treated with either hemodialysis or CAPD. Griva et al. studied 77 hemodialysis patients and 68 peritoneal dialysis patients, and Buoncristiani studied 15 hemodialysis patients and 18 peritoneal dialysis patients. Griva et al. and Buoncristiani et al. administered tests to both groups up to two hours before the hemodialysis was administered; peritoneal dialysis patients were tested at the same time

for control purposes. In both studies, tests were repeated after hemodialysis was administered to both groups. In Griva et al. tests were repeated 24 hours after hemodialysis, and in Buonchristiani tests were repeated two hours after hemodialysis was administered. Therefore, these studies must be considered separately. Griva administered four neurocognitive tests potentially relevant to the safe operation of a motor vehicle, while Buoncristiani administered three. We categorized these tests in the domains of general neurocognitive function, attention and concentration, visuospatial skills, and executive function.

Findings between and within the two studies conflicted, with some test results showing significant differences between dialysis treatment groups, and other test results not. In the following text, we present the studies' findings, divided by domain. Following that, the studies' data and the P-scores we calculated are shown in Table 38.

General

Mini Mental State Examination: Buoncristiani et al. administered the Mini Mental State Examination to 15 hemodialysis and 22 peritoneal dialysis patients up to two hours before and again two hours after a hemodialysis session. No statistically significant difference was observed between groups at either time point.

Attention and Concentration

Trail Making Test A: Griva administered the Trail Making Test A up to two hours before and one day after hemodialysis to 77 hemodialysis patients and 68 peritoneal dialysis patients. The difference between groups was not statistically significant at either time point. However, the evidence provided by a single study is of insufficient quantity to form a conclusion.

Digit Span: Buoncristiani et al. administered the Digit Span test up to two hours before and up to two hours after hemodialysis sessions for 15 hemodialysis patients and a control cohort of 22 peritoneal dialysis patients. A statistically significant difference in scores between the two groups was detected both before and after hemodialysis was administered.

Symbol Digit Modalities Test: Griva et al. tested 77 hemodialysis patients and 68 peritoneal dialysis patients on the written and oral Symbol Digit Modalities test up to two hours before and one day after hemodialysis treatment. The difference in scores between groups was not significant at either time point.

Number Connection Test: The Number Connection Test was administered to 15 hemodialysis patients and 22 peritoneal dialysis patients up to two hours before and two

hours after hemodialysis treatment in Buoncristiani's study. The difference between test scores of hemodialysis patients and peritoneal dialysis patients before hemodialysis administration was statistically significant. The difference after hemodialysis was not significant. This suggests that hemodialysis patients perform more poorly on this test than peritoneal dialysis patients before hemodialysis is administered, but that after hemodialysis, the hemodialysis patients' scores improve and are no longer significantly different from the peritoneal dialysis patients' scores.

Visuospatial Skills

Benton Visual Retention Test: One study, Griva et al., administered the Benton Visual retention test. In this study, the scores of 77 hemodialysis patients were significantly different than those of 68 peritoneal dialysis patients both before and after hemodialysis administration. However, conclusions cannot be drawn from a single study.

Executive Function

Trail Making Test B: Griva administered the Trail Making B tests up to two hours before hemodialysis and detected a statistically significant difference in scores between the 77 hemodialysis patients and 68 peritoneal dialysis patients. The day after hemodialysis, the difference was not statistically significant. These findings suggest that, compared with peritoneal dialysis controls, dialysis patients fare more poorly on this measure of executive function.

Grooved Pegboard Test: The Grooved Pegboard test was administered to both the dominant and nondominant hands of 77 hemodialysis and 68 peritoneal dialysis patients. The test was administered up to two hours before and one day after hemodialysis in both groups. No statistically significant difference was found at either time point.

Table 38. Neurocognitive Function of Hemodialysis Patients and Peritoneal Dialysis Patients

Domain	Test	Study	Year	Hemodialysis			Peritoneal Dialysis			SMD (95% CI)	P=	Bottom Line: Difference Between Groups?
				N=	Mean	SD	N=	Mean	SD			
General	Mini Mental State Examination	Buoncristiani et al.(137)	1992	15 Before HD	25.5	1.2	22	26.6	2.2	0.054 (-0.604–0.710)	0.873	No
				15 After HD	27	1.4	22	26.6	2.2	0.208 (-0.45–0.866)	0.535	No
Attention and Concentration	Trail Making Test A	Griva et. al.(132)	2003	77 Before HD	53.73	37.32	68	50.49	25.98	0.100 (-0.227–0.426)	0.549	No
				77 After HD	45.13	35.34	68	46.60	26.35	0.144 (-0.183–0.471)	0.387	No
	Digit Span	Buoncristiani et al.(137)	1992	15 Before HD	5.7	1.9	22	9.4	1.7	2.076 (1.267–2.884)	<0.001	Yes
				15 After HD	8.3	1.7	22	9.4	1.7	3.346 (2.340–4.352)	<0.001	Yes
	Symbol Digit Modalities Test—Written	Griva et. al.(132)	2003	77 Before HD	40.92	12.96	68	41.31	12.66	0.030 (-0.296–0.357)	0.855	No
				77 After HD	47.10	15.20	68	44.73	14.56	0.159 (-0.168–0.486)	0.340	No
	Symbol Digit Modalities Test—Oral	Griva et. al.(132)	2003	77 Before HD	45.82	14.22	68	44.91	13.24	0.066 (-0.260–0.392)	0.691	No
				77 After HD	52.10	16.58	68	48.61	15.87	0.215 (-0.112–0.542)	0.198	No
	Number Connection Test	Buoncristiani et al.(137)	1992	15 Before HD	88.2	29.3	22	64.3	24.8	0.895 (0.208–1.583)	0.011	Yes
				15 After HD	67.1	18	22	64.3	24.8	0.125 (-0.532–0.782)	0.708	No
Visuospatial Skills	Benton Visual Retention Test—Correct	Griva et. al.(132)	2003	77 Before HD	5.08	2.30	68	4.75	1.98	0.487 (0.156–0.818)	0.004	Yes
				77 After HD	5.97	2.31	68	4.97	1.74	0.485 (0.154–0.816)	0.004	Yes
	Benton Visual Retention Test—Errors	Griva et. al.(132)	2003	77 Before HD	8.64	5.46	68	8.47	4.51	0.034 (-0.292–0.360)	0.839	No
				77 After HD	6.61	5.30	68	7.82	3.85	0.259 (-0.069–0.586)	0.122	No

Executive Function	Trail Making Test B	Griva et. al.(132)	2003	77 Before HD	97.92	51.72	68	50.49	25.98	1.138 (0.786–1.489)	<0.001	Yes
				77 After HD	45.13	32.34	68	46.60	26.35	0.050 (-0.277–0.376)	0.766	No
	Grooved Pegboard Test—Dominant hand	Griva et. al.(132)	2003	77 Before HD	88.66	29.78	68	93.65	34.28	0.156 (-0.171–0.483)	0.349	No
				77 After HD	85.12	28.81	68	91.95	32.16	0.192 (-0.135–0.519)	0.251	No
	Grooved Pegboard Test —on dominanant hand	Griva et. al.(132)	2003	77 Before HD	100.19	34.59	68	104.61	43.64	0.113 (-0.213–0.439)	0.497	No
				77 After HD	95.40	34.31	68	103.25	39.71	0.213 (-0.115–0.540)	0.203	No

HD: Hemodialysis
CAPD: Continuous ambulatory peritoneal dialysis

Drugs

Two publications assessed the effect of the use of drugs on neurocognitive function in dialysis patients. Marsh et al.(126) tested the neurocognitive function of 24 ESRD patients with anemia on hemodialysis before, and 3 and 12 months after initiating recombinant human erythropoietin (rHuEPO) treatment began. Altmann et al. studied the neurocognitive effects of administering lanthanum carbonate in 174 hemodialysis patients compared with standard phosphate-binder therapy in 178 hemodialysis patients for two years.(138) Because there are only two studies reporting a small number of outcomes in this evidence base, we discuss their findings in the text below rather than presenting data in tables.

Attention and concentration

Symbol-digit modalities test: Marsh et al.(126) found a statistically significant improvement in mean scores from baseline (39.3±11.5; n=17) to month 3 (45.5±11.4; n=18; *P*=0.37) and month 12 of treatment (47.0±12.0; n=15; *P*=0.003) in patients taking rHuEPO. This study suggests that hemodialysis patients with anemia benefit from rHuEPO.

Digit Vigilance—Percentage of Targets Detected Test: Comparing the test results of hemodialysis patients on lanthanum carbonate and standard phosphate binder, Altmann et al.(138) detected a statistically significant difference (P=0.028) on this test in favor of lanthanum carbonate, but did not find a significant difference on other tests, including *Simple Reaction Time* (P=0.45), *Digit Vigilance–Response Time* (P=0.69), or *Choice Reaction Time* (P=0.1681) tests.

Executive function

Trail Making Test B: Marsh et al.(126) did not find statistically significant mean improvements in time to completion from baseline (113.4±57.5; n=18) to month 3 (112.6±63.9; n=18; *P*=0.900) or month 12 (92.5±51.1; n=15; *P*=0.135). ECRI Institute calculated *P*-values assuming a correlation coefficient of 0.50.

Key Question 3 Part C: Indirect Evidence—Dialysis and Sleep

This section assesses the prevalence and severity of sleep disorders in patients with ESRD requiring dialysis, and associates those factors with potential increased crash risk. As discussed in the background section, individuals with ESRD have an especially high prevalence of sleep disorders. The prevalence of sleep apnea in patients with ESRD is up to 25 times that of the general population. As excessive daytime sleepiness has an intuitive relationship with crash risk and sleep apnea has been associated with increased crash among commercial and non-CMV drivers, sleep-related disorders are of particular interest in this report. However, these data should not be construed as a perfect substitute for actual crash data.

Search Strategy

Our search strategy to identify studies on the relationship between dialysis and sleep disorders is detailed in Appendix A. These searches identified 27 potentially relevant abstracts. Based on our retrieval criteria (Appendix B), we retrieved 12 in full length. Upon examination of the full-length articles, we found that 9 studies did not meet inclusion criteria (Appendix C). The 9 excluded studies and the reasons for their exclusion are listed in Appendix D, Table D-3. The remaining 3 studies were included in the assessment. The process used to develop the evidence base for Key Question 3: Part C is shown in Figure 14. Included studies are listed in Table 39.

Figure 14. Development of Evidence Base for Key Question 3 Part C: Sleep-Related Evidence

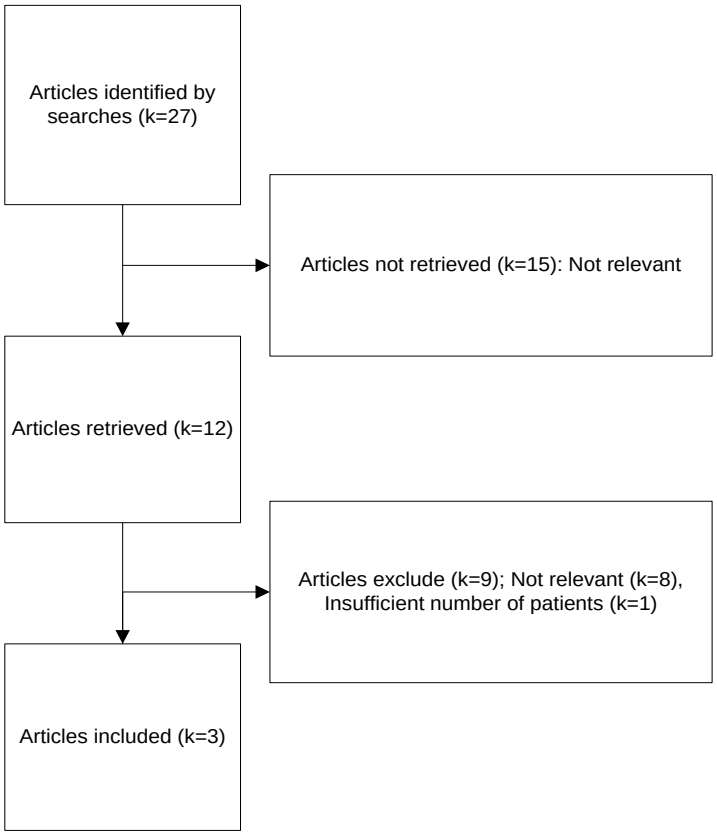


Table 39. Evidence Base for Key Question 3 Part C: Sleep-Related Evidence

Reference	Year	Study Location	Country
Unruh et al.(130)	2006	Pittsburgh, PA	USA
Hanley and Pierratos(140)	2001	Toronto	Canada
Jean et al.(82)	1995	Not reported	France

Evidence Base

This subsection briefly describes the main attributes of the studies that make up the evidence base for Key Question 3, Sleep-related Evidence. Here we discuss the quality of the included studies, and the generalizability of each study's findings to CMV drivers.

Characteristics of Included Studies

The studies in this section assessed the prevalence or severity of sleep disorders in individuals with chronic kidney disease. These studies may provide important

information on the sleep-related function of people with chronic kidney disease; however, they cannot be considered a perfect substitute for crash risk among motor vehicle drivers. While the sleep tests attempt to measure factors that have the potential to affect driving, the actual relationship between these factors and crash risk is unknown.

The primary characteristics of the three included studies that address Key Question 3: Sleep-related Evidence, are presented in Table 40. All three studies were prospective, but they had different designs and different outcomes of interest. Two compared indicators of sleep disturbance in the same cohort before and after changing dialysis treatment approach, one compared indicators of sleep disturbance in one cohort at different time points, and the remaining study examined the enrolled patients at one time point. Only one study compared scores of patients on hemodialysis to scores of a control group.(130)

Table 40. Key Study Design Characteristics of Studies That Address Key Question 3 Part C: Sleep-Related Evidence

Study	Year	Severity of Renal Failure	Severity Level Definition	Prospective or Retrospective	Study Design Type	Comparison
Unruh et al.(130)	2006	Severe	Patients on dialysis	Prospective	Cohort Controlled	Participants in Sleep Heart Health Study
Hanley and Pierratos(140)	2001	Severe	Patients on dialysis	Prospective	Pre–post	Scores were compared before and after patients switched from conventional hemodialysis to overnight hemodialysis
Jean et al.(82)	1995	Severe	Patients on dialysis	Prospective	Randomized controlled trial	PSG recordings of patients on different dialysate buffers were compared in the same group of patients on different days

We assessed the quality of the studies in the evidence base using the Revised Newcastle–Ottawa Quality Scales for Cohort Studies, the ECRI Institute Quality Scale for Controlled Trials, and the ECRI Institute Quality Scale for Pre–Post Studies. This evidence base was not of high quality. The quality ratings for each study used and the instrument used to assess them are shown in Table 41. For the full itemized quality assessment for each study, refer to Appendix F.

Table 41. Quality of the Studies That Assess Key Question 3 Part C: Sleep-Related Evidence

Reference	Year	Quality Scale Used	Quality Category
Unruh et al.(130)	2006	Revised New Castle–Ottawa Quality Scale for Cohort-controlled Studies	Moderate
Hanley and Pierratos(140)	2001	ECRI Institute Quality Scale for Pre–Post Studies	Moderate
Jean et al.(82)	1995	ECRI Institute Quality Scale for Controlled Trials	Low

Generalizability of Evidence Base to Target Population

This subsection details the extent to which the individuals enrolled in the studies that address Key Question 3: Sleep-related evidence are similar to CMV drivers in the United States. However, there is very limited demographic information provided in the included studies to determine how comparable the enrolled individuals are to CMV drivers. Most important, none of the articles stated that CMV drivers were enrolled. None of the articles reported on the employment status of enrolled patients, drivers' license type, or driving exposure. Mean ages ranged from mid 40s to early 60s. The prevalence of men was 70 percent or higher. Despite the predominance of men in this sample, women are still somewhat overrepresented compared with the gender distribution in CMV drivers. With these factors taken into account, the generalizability of the patients in these studies to CMV drivers is unclear. Important characteristics of the individuals included in the studies that address Key Question 3 Part C are presented in Table 42.

Table 42. Generalizability of Studies That Address Key Question 3 Part C: Sleep-Related Evidence

Reference	Year	(Number of Individuals With Kidney disease Included (n=)	Duration of kidney disease	% Male	% CMV Drivers	Mean Age (SD) in Years	Driving Exposure	% with Medically Restricted Licenses	Generalizability to Target Population
Unruh et al.(130)	2006	46	NR; median duration of dialysis 22 months	72%	NR	62.7 (NR)	NR	NR	Unclear
Hanley and Pierratos(140)	2001	14	NR; Range of duration on dialysis 1–15 years	71%	NR	45 (9)	NR	NR	Unclear
Jean et al.(82)	1995	10	NR; Mean months on dialysis 26	70%	NR	53.3 years	NR	NR	Unclear

NR not reported; SD standard deviation.

Findings

Three studies reported on sleep disorders in individuals requiring dialysis, however, the differences among them in study designs and outcomes means that each study must be considered in isolation. Therefore, we report outcomes and findings for each study separately in the paragraphs below. The studies are presented in descending order by publication date.

Study of Unruh and Colleagues

Unruh et al. (2006) compared sleep apnea prevalence and severity in a sample of 46 hemodialysis patients and 137 participants in SHHS.(130)—a prospective cohort–control study to assess the relationship between sleep-disordered breathing and cardiovascular disease. Patients with known sleep disorders or who were taking related treatment were excluded from this study. Study participants were matched for age, gender, BMI and ethnicity (black or not black).

All patients enrolled in the study completed surveys and underwent in-home technician-assisted partial channel PSG. In-laboratory PSG is the current reference standard study for diagnosing and determining the severity of obstructive sleep apnea. Among other physiological parameters such as air flow, heart rate and rhythm, and respiratory effort, PSG assesses all four of the known risk factors for crash among drivers with sleep apnea, which were identified in a previous FMCSA evidence report, "Obstructive Sleep Apnea and Commercial Motor Vehicle Driver Safety." These risk factors for crash are: BMI, severity of apnea and hypopnea (as measured using HDI or RDI), presence and severity of oxygen desaturation, presence and severity of excessive daytime sleepiness.

The differences between groups in sleep efficiency (sleep time vs. total time in bed), proportion of sleep in Stage 1 and Stage 2, and daytime sleepiness as measured by the Epworth Sleepiness Scale were not statistically significant. However, hemodialysis patients scored statistically significantly more poorly on many other measurements, including: sleep time, proportion of patients who had REM sleep, arousals per hour, respiratory disturbance, hypoxemic index, and lowest oxygen saturation during both REM and non-REM. Based on these findings, Unruh and colleagues concluded their findings supported an association between hemodialysis and sleep-disordered breathing. Compared with matched controls, the odds of having severe sleep-disordered breathing is four-fold higher among hemodialysis patients.

Study of Hanly and Pierratos

Hanly and Pierratos (2001) enrolled 14 of 15 consecutive patients on conventional hemodialysis. None of the patients was asked if he or she had any sleep disorders. Overnight laboratory PSG was administered to all patients to assess prevalence and severity of sleep apnea. Following PSG, all of the patients' hemodialysis was switched from three four-hour sessions per week to nocturnal dialysis for eight hours, six to seven nights per week. After a range of 6 to 15 months (depending on the patient), PSG was repeated to determine whether the prevalence or severity of sleep disorders changed.

The initial PSG testing determined a 57 percent prevalence of sleep apnea. Only one of the eight patients had been diagnosed with sleep apnea prior to the study. One additional patient was diagnosed with Cheyne-Stokes respiration with an estimated left ventricular fraction ejection of 50 percent. Following treatment change to nocturnal hemodialysis, patients showed statistically significant mean improvement in the total number of episodes of apnea and hypopnea per hour of sleep and oxygen saturation during sleep. Outcomes for which a statistically significant change was not observed include: total sleep time, sleep efficiency, stage of sleep, REM sleep, arousals per hour, periodic leg movements per hour, and transcutaneous partial pressure of carbon dioxide. The findings of this study suggest that the prevalence of sleep apnea may be very high among people with ESRD, and that dialyzing patients overnight may improve their sleep symptoms.

Study of Jean and Colleagues

Jean and colleagues (1995) administered acetate buffer during one hemodialysis session and bicarbonate buffer during another hemodialysis session to 10 patients. Each night, they collected sleep and ventilation data from both groups in a sleep laboratory using PSG. In addition, they administered questionnaires. In their analysis, the researchers compared the scores associated with the different buffer.

The authors reported no significant differences in arterial pH, oxygen saturation, partial pressure of carbon dioxide, or hydrogen carbonate. They found sleep duration was short and fragmented on both nights, but significantly shorter following bicarbonate buffer. No differences in sleep architecture or slow-wave sleep were observed. Significantly more episodes of disordered breathing (hypopnea episodes and central apnea episodes) were observed following bicarbonate buffer.

The meaning of the findings from this study is unclear. Differentiating the effects of the different buffers from the repeated testing, two sessions in a row, is not possible. Furthermore, it is not possible to tell whether sleep would be affected long term. As patients with chronic ESRD typically require long-term dialysis, this is a more relevant question to investigate. No conclusions can be drawn from this study because of these weaknesses in study design, and because these findings were not replicated in any other study we identified.

Section Summary

There is currently no direct evidence associating dialysis and the risk for a motor vehicle crash. However, indirect evidence indicates that it is plausible that drivers with ESRD treated with dialysis and related medications may be at an increased crash risk. (Strength of Conclusion: Minimally Acceptable).

Direct Evidence – Crash Studies*: Our searches identified no studies.*

Indirect Evidence – Studies Neurocognitive Function*: Thirteen studies with 980 patients with unclear generalizability to CMV drivers were identified. Overall, this evidence base was of low quality. The included studies used a variety of study designs and different control populations, limiting their comparability and compatibility for statistical analysis. Furthermore, studies infrequently reported the same outcomes. For analysis, we subdivided the studies by the comparisons they made. No clear trend emerged from these 13 studies to definitively conclude that patients treated with dialysis do or do not have neurocognitive impairment compared with controls. However, a substantial number of test results suggest that patients treated with dialysis do have neurocognitive impairment in domains associated with an increased risk of motor vehicle crash. Findings also suggest that ESRD patients on hemodialysis may be more impaired than patients not on dialysis, and that patients on hemodialysis may be more impaired the day before dialysis than the day after.*

Indirect Evidence—Studies of Sleep-Related Outcomes*: Three studies with a total of 70 patients were identified for this evidence base. Each addressed different outcomes and therefore had to be considered in isolation. The findings of two studies point to an association between sleep disorders and kidney disease, indirectly suggesting an increased risk of motor vehicle crash among dialysis patients. The findings of one also suggest that overnight (nocturnal) dialysis may alleviate sleep apnea. The findings of the third study suggest that different dialysis buffers may alleviate symptoms.*

Key Question 4. Is Kidney transplantation, and Accompanying Drug Treatment, Associated With an Increased Crash Risk?

Kidney transplantation is the treatment of choice for individuals with chronic ESRD, and (when successful) it provides independence from dialysis long term. This independence may permit return to work and other improvements in quality of life. However, renal function may still be impaired in some recipients, so they may still suffer some symptoms of kidney disease. These symptoms could put drivers with kidney transplant at risk for motor vehicle crash.

Individuals with kidney transplants must carefully follow their immunosuppression regimen to minimize risk of transplant rejection. Although these drugs make successful kidney transplantation possible, they may have adverse effects, such as inducing sleepiness. Such effects may also compromise safe operation of a motor vehicle.

We assessed the association between kidney transplantation and accompanying drug treatment in three ways. First, we searched for evidence directly associating kidney

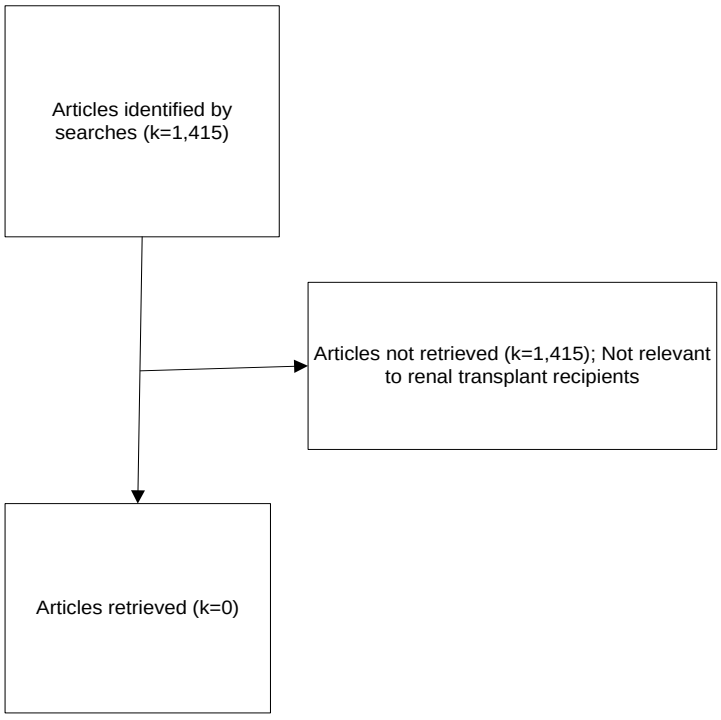
transplantation and motor vehicle crash. Second, we looked to evidence on performance of kidney transplant recipients on neurocognitive function in domains previously identified as related to crash. Finally, we sought evidence associating ESRD and sleep disorders, as sleep disorders have been associated with increased risk of motor vehicle crash. The latter two measurements provide indirect evidence of the potential for crash among transplant recipients. However, they do not provide a perfect substitute for actual crash data.

Key Question 4 Part A: Direct Evidence—Kidney transplantation and Crash Risk

Identification of Evidence Base

To meet the aims of this section, we searched for comparative trials that looked at crash risk among individuals who have received a kidney transplant and individuals who have not. Our search strategy is detailed in Appendix A. These searches identified 1,415 abstracts. Based on our retrieval criteria (Appendix B), we did not retrieve any in full length, as none pertained to crash risk in transplant recipients. Therefore, we could not proceed with the analysis of direct evidence of crash and kidney transplantation.

Figure 15. Development of Evidence Base for Key Question 4 Part A: Direct Evidence



Key Question 4 Part B: Indirect Evidence—Kidney transplantation and Neurocognitive Function

Identification of Evidence Base

In addition to searching for studies reporting direct evidence of a relationship between kidney transplantation and motor vehicle crash, we searched for comparative trials that compared neurocognitive function among individuals who have received a kidney transplant and otherwise comparable individuals who have not received kidney transplantation. Recognizing that "no single test can be used to predict the effect of a drug on cognition or on the diverse and complex skills involved in everyday tasks, such as driving a car,"(141) in this section we assessed the cognitive and psychomotor tests that might be most relevant to assessments of driving skills. Findings from these tests are not a perfect surrogate for actual crash data; however, in the absence of such data they provide meaningful information.

Our search strategy is detailed in Appendix A. These searches identified 15 abstracts. Based on our retrieval criteria (Appendix B), we retrieved two in full length. This process is illustrated in Figure 6. Upon full examination, both satisfied our inclusion criteria. The two included studies are listed in Table 43.

Figure 16. Development of Evidence Base for Key Question 4 Part B: Neurocognitive Evidence

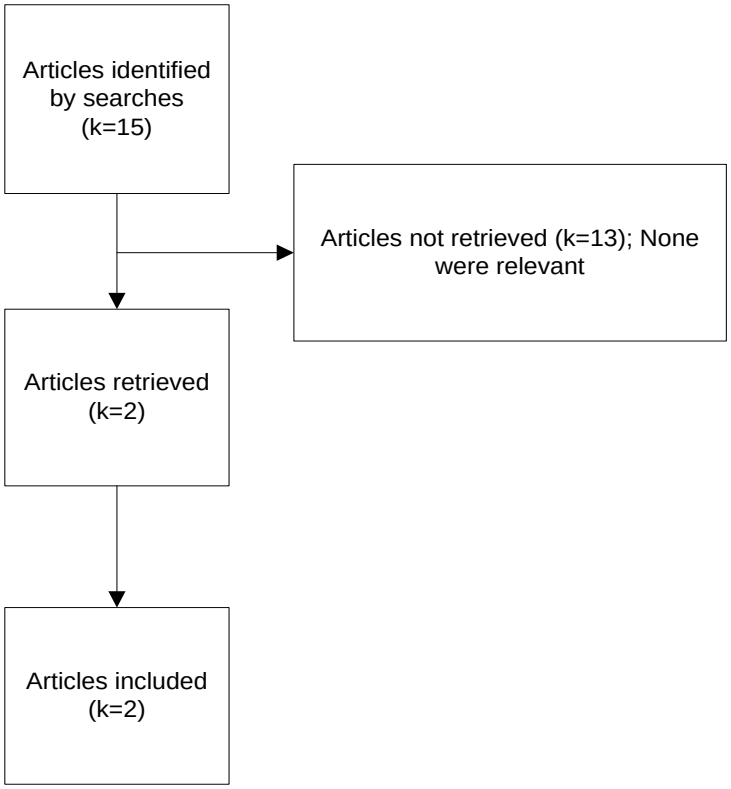


Table 43. Evidence Base for Key Question 4: Neurocognitive Evidence

Reference	Year	Study Location	Country
Griva et al.(139)	2003	Not reported	UK
Kramer et al.(127)	1996	Not reported	Austria

Evidence Base

This subsection briefly describes the main attributes of the studies that make up the evidence base for Key Question 4, neurocognitive evidence— the quality of the included studies, and the generalizability of each study's findings to CMV drivers.

Characteristics of Included Studies

The two identified studies are of different design types. Griva et al. compared neurocognitive function of 28 patients with ESRD before and after transplantation, and compared their data with normative (historical control) data.(134) Kramer et al. compared the neurocognitive function of 15 ESRD patients with matched healthy controls before and after the patients underwent kidney transplantation.(127)

Table 44. Key Study Design Characteristics of Studies That Address Key Question 4 Part B: Neurocognitive Evidence

Reference	Year	Severity of Kidney disease	Severity Level Definition	Prospective or Retrospective	Study Design Type	Comparison
Griva et al.(139)	2003	Severe	Requiring hemodialysis; patients subsequently underwent transplantation	Prospective	Observational (pre-post); Cross-sectional comparative	Pre–post transplantation scores; Normative data
Kramer et al.(127)	1996	Severe	Requiring hemodialysis; patients subsequently underwent transplantation	Prospective	Observational (pre–post); Cohort control	Pre–post transplantation scores Matched healthy controls

To assess the quality of outcomes reported by the two studies included in this evidence base, we used the Revised Newcastle–Ottawa Cohort Control Quality Assessment Scale, and the ECRI Institute Pre–Post Quality Scale. None of the outcomes was rated high in quality. The quality assessment category for both included studies is shown in Table 45. For full itemized quality assessments, refer to Appendix G.

Table 45. Quality of the Studies That Assess Key Question 4 Part B: Neurocognitive Evidence

Reference	Year	Quality Scale Used	Quality Category
Griva et al.(139)	2003	ECRI Institute Quality Scale for Pre–Post Studies	Low
		Revised Newcastle–Ottawa Cohort Control Quality Assessment Scale	Moderate
Kramer et al.(127)	1996	ECRI Institute Quality Scale for Pre–Post Studies	Low
		Revised Newcastle–Ottawa Cohort Control Quality Assessment Scale	Moderate

Generalizability of Evidence Base to Target Population

This subsection details the extent to which the individuals enrolled in the studies that address Key Question 4 are similar to CMV drivers in the United States. However, very limited demographic information is provided in the included studies to determine how comparable the enrolled individuals are to CMV drivers. Most important, none of the articles state that CMV drivers were enrolled. Neither article reported drivers' license type or driving exposure. Kramer et al. did not report on patients' employment status, but Griva and colleagues did. In that study, 64.3 percent of patients were able to work, and 57.1 percent were either working or a student. The mean age in both studies was mid-40s. In one study, more than half of the patients were male, in the other, slightly less than half were. These samples have a disproportionate number of females compared with the commercial driver population.

Table 46. Generalizability of Studies That Address Key Question 4 Part B: Neurocognitive Evidence

Reference	Year	(Number of Individuals with Kidney disease Included (n=)	Duration of Kidney disease	% Male	% CMV Drivers	Mean Age (SD) in Years	Driving Exposure	% with Medically Restricted Licenses	Generalizability to Target Population
Griva et al.(139)	2003	28	NR: Duration of dialysis 2.6 (2.7) years	57.1%	NR	44.0 (12.01)	NR	NR	Unclear
Kramer et al.(127)	1996	15	NR: Duration of dialysis 1.5 years (range 3 months – 8 years)	46.7%	NR	45 (13)	NR	NR	Unclear

Findings

The two included studies assessed several neurocognitive functions relevant to driving, with only one test in common. We grouped the tests into three broader categories: general, attention and concentration, and executive function. Listed in Table 47 are the specific tests used in the identified studies to assess neurocognitive function of kidney transplantation recipients.

Table 47. Outcomes Reported for Key Question 4 Part B: Neurocognitive Evidence

Study	Year	General	Attention and Concentration		Executive Function	
		MMSE	Trail Making Test A	Symbol–digit Modality test	Trail Making Test B	Grooved Pegboard Test
Griva et al.(139)	2003		✓	✓	✓	✓
Kramer et al.(127)	1996	✓	✓			

In the following text we describe the results of the tests listed in Table 47, divided by domain category. Owing to the small quantity of data, we provide data in text but not tables. Mean scores with standard deviations are reported in the text. ECRI Institute calculated all *P*-values for Kramer et al.. For pre–post data, we used a correlation coefficient of 0.5.

General

Kramer et al. administered the (MMSE to 45 healthy subjects and 15 transplant patients before and after transplantation.(127) While on dialysis, the mean score of the 15 patients (mean 28.5±2.0) had a statistically significantly poorer test result than healthy subjects (mean 29.5±0.8; *P*=0.007). After kidney transplantation, the test was re-administered to

the 15 patients (mean 29.1±0.9) and was no longer significantly different from that of the healthy control group (*P*=0.108). However, the difference pre–post in the same group of patients was not significant (*P*=0.193).

Attention and Concentration

Two tests were administered to assess the attention and concentration of transplant recipients: the Trail Making Test A and the Symbol-Digit Modality Test.

Trail Making Test A: Both included studies administered the trail making test. Kramer et al. found that the mean score of the 15 enrolled patients was significantly lower than controls (29±8) before patients underwent transplantation (34±10 seconds; *P*=0.33), but not after transplantation (28±9; *P*=0.702). The difference before and after transplantation was significant (*P*=0.049) Griva et al. also reported the mean score of 28 patients before (37.83±19.05) and after transplantation (32.49±17.48) and did not detect a significant difference (P=0.960).(134) Five patients (17 percent) in that study had scores suggestive of a deficit compared with normative data, however, the size of the effect between groups was not reported.

Symbol-Digit Modality Test: Griva et al. administered this test to 28 patients before and after kidney transplantation. For the written segment, the mean score before (49.43±14.45) transplantation was not significantly different from the mean score after transplantation (53.29±13.71; *P*=0.061). For the oral segment, the difference between mean pre (52.68±14.34) and post (59.19±15.18) was not statistically significant (*P*=0.160). Before transplantation, seven patients (25 percent) were impaired on the writing subtest and eight patients (29 percent) were impaired on the oral subtest. Following transplantation, five patients (18 percent) were impaired on each test. Neither change was statistically significant.(134) These findings suggest that the neurocognitive performance of patients with kidney disease may not improve substantially following kidney transplantation.

Executive Function

Griva et al.(134), assessed executive function using the Trail Making Test B and the Grooved Pegboard Test before and after transplantation in 28 people.

Trail Making Test B: The difference between mean pre (77.45±35.12) and post (77.20±41.81) transplantation scores was not statistically significant (*P*=0.630). The number of people impaired on the test was four (14 percent) for both pre and post results: this difference was not significant.(134)

Grooved Pegboard Test: The difference between mean pre and post scores on the grooved pegboard test was not significant for either the nondominant hand (86.31±27.73 pre to 75.28±22.56 post; *P*=0.995) or dominant hand (78.63±21.61 pre to 75.28±22.56 post; *P*=0.342).(134)

Key Question 4 Part C: Indirect Evidence—Kidney transplantation and Sleep

This section assesses the prevalence and severity of sleep disorders in patients who have undergone kidney transplantation. Individuals with ESRD treated with dialysis have an especially high prevalence of sleep disorders, up to 25 times that of the general population. The contributions of confounding factors (such as age or etiology), the kidney disease process, and treatments to onset and severity of sleep disorders are unclear. Therefore, it is unclear whether sleep impairment should be expected to improve following kidney transplantation. This section assesses the relationship between sleep disorders and renal failure treated with transplantation.

As noted previously, sleep disorders have been associated with increased crash risk. As excessive daytime sleepiness has an intuitive relationship with crash risk, and sleep apnea has been associated with increased crash among commercial and non-CMV drivers, sleep-related disorders are of particular interest in this report. These studies may provide important information on the sleep-related function of people with kidney transplantation; however, they cannot be considered a perfect substitute for crash risk among motor vehicle drivers. While the sleep tests measure factors that have the potential to affect driving, the actual relationship between these factors and crash risk is unknown.

Search Strategy

Our search strategy to identify studies on the relationship between dialysis and sleep disorders is detailed in Appendix A. These searches identified 27 potentially relevant abstracts. Based on our retrieval criteria (Appendix B), we retrieved three full-length articles. Upon examination of the full-length articles, we found that two did not meet the inclusion criteria (Appendix C). The two excluded studies and the reason for their exclusion are in Appendix D, Table D-4. The remaining study was included. The process used to develop the evidence base for Key Question 3: Sleep-related Evidence is shown in Figure 17. The included study is in Table 48.

Figure 17. Development of Evidence Base for Key Question 4: Sleep-Related Evidence

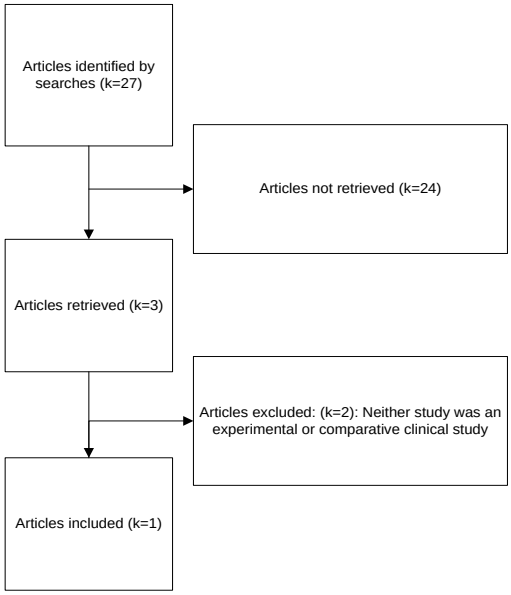


Table 48.Evidence Base for Key Question 4 Part C: Sleep-Related Evidence

Reference	Year	Study Location	Country
Molnar et al.(142)	2007	Budapest	Hungary

Evidence Base

This subsection briefly describes the main attributes of the study that makes up the evidence base for Key Question 4: Sleep-related Evidence—its quality and the generalizability of the study's findings to CMVdrivers of .

Characteristics of Included Studies

The study in this section assessed the prevalence and severity of sleep disorders in 841 individuals with chronic renal failure who underwent kidney transplantation and in 175 patients awaiting a transplant. The primary characteristics of the included study that addresses Key Question 4: Part C are presented in Table 49.

Table 49.Key Study Design Characteristics of Studies That Address Key Question 4 Part C: Sleep-Related Evidence

Study	Year	Severity of Renal Failure	Severity Level Definition	Prospective or Retrospective	Study Design Type	Comparison
Molnar et al.(142)	2007	Severe	Requiring transplantation	Prospective	Cohort	Patients waiting for kidney transplantation

We assessed the quality of the included study using the Revised Newcastle–Ottawa Quality Assessment Scale for Cohort Studies. The quality category of the only study, and therefore of the evidence base, was moderate. For an itemization of the quality assessment, please see Appendix F. For a summary of the quality assessment, see Table 50.

Table 50. Quality of the Studies that Assess Key Question 4 Part C: Sleep-Related Evidence

Reference	Year	Quality Scale Used	Quality Category
Molnar et al.(142)	2007	Revised Newcastle–Ottawa Quality Assessment Scale for Cohort Studies	Moderate

Generalizability of Evidence Base to Target Population

This subsection details the extent to which the individuals enrolled in the study that addresses Key Question 4: Part C are similar to CMV drivers in the United States. However, there is very limited demographic information provided in the included studies to determine how comparable the enrolled individuals are to CMV drivers. Most important, the article did not state that CMV drivers were enrolled. It did not report on the employment status of enrolled patients, drivers' license type, or their driving exposure. The mean age was 49 years. Fifty-nine percent of the participants were men, which overrepresents women compared with CMV driver populations. With these factors taken into account, the generalizability of the patients in these studies to CMV drivers is unclear. Important characteristics of the individuals included in the studies that address Key Question 4: Sleep-related Evidence, are presented in Table 42.

Table 51. Generalizability of Studies That Address Key Question 4 Part C: Sleep-Related Evidence

Reference	Year	(Number of Individuals with Kidney disease Included (n=)	Duration of Kidney disease	% Male	% CMV Drivers	Mean Age (SD) in Years	Driving Exposure	% with Medically Restricted Licenses	Generalizability to Target Population
Molnar et al.(142)	2007	1,016	NR	59%	NR	49 (NR)	NR	NR	Unclear

CMV Commercial motor vehicle; NR Not reported.; SD Standard deviation.

Findings

Molnar and colleagues enrolled 841 kidney transplant recipients and 175 patients with ESRD awaiting kidney transplantation. All patients were assessed for signs and symptoms suggestive of obstructive sleep apnea using the Berlin Sleep Apnea

Questionnaire. Information on variables related to sleep apnea, such as BMI and comorbidity, was collected from charts and interviews.

The study authors found that 27 percent of transplant recipients and 33 percent of the wait-listed group were 'at risk' for sleep apnea. This difference was not statistically significant. Factors significantly associated with high risk for sleep apnea among transplant recipients included: older age, male gender, fewer years of education, no or fewer comorbid conditions, diabetes, cerebrovascular disease, heart disease, serum CRP, GFR, and intake of hypnotic drugs. Factors not associated with increased risk were serum albumin, serum hemoglobin, cumulative median duration of ESRD, duration of transplantation, and different immunosuppressive drugs.

The findings of this study suggest that the prevalence of sleep apnea among patients with ESRD awaiting transplantation is not significantly different than that of transplant recipients. Among transplant recipients, a number of factors were associated with risk level for apnea. Of medications, hypnotic drugs were associated with an increased risk level for sleep apnea, but immunosuppressants were not.

Section Summary

Currently, there is no direct evidence associating kidney transplantation and motor vehicle crash risk. However, indirect evidence suggests the possibility that kidney transplant recipients may be at a lower risk for motor vehicle crash than individuals with ESRD treated with dialysis (Strength of Conclusion: Minimally Acceptable).

Direct Evidence – Crash Studies: *No studies were identified by our searches.*

Indirect Evidence – Neurocognitive Function: *Two low-quality studies that enrolled a total of 43 kidney transplant recipients met the inclusion criteria for this key question and reported on neurocognitive function. One study observed significant improvements in neurocognitive function among kidney transplant recipients across several domains. The second also observed some small improvements in neurocognitive function, but these improvements were not statistically significant. Given the small size of this study, the lack of a statistically significant finding is not surprising. This finding may be an example of a type-II statistical error. Neither of these studies specifically enrolled individuals from a population of CMV drivers. Consequently, the generalizability of the findings of these two studies to CMV drivers is unclear.*

Indirect Evidence—Sleep-Related Outcomes: *One low-quality study that enrolled 841 kidney transplant recipients met the inclusion criteria for this key question and reported on a sleep-related outcome. This study was of low quality and unclear relevance to CMV*

drivers. The findings of this study suggest that a substantial portion of kidney transplant recipients may be at risk for sleep apnea, and therefore at increased risk of motor vehicle crash. However, a smaller proportion of kidney transplant recipients were at risk for sleep apnea compared with similar individuals on dialysis, suggesting that the risk of motor vehicle crash among transplant recipients may be lower among transplant recipients than dialysis patients.

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Appendix A: Search Summaries

Kidney disease

The search strategies employed combinations of freetext keywords as well as controlled vocabulary terms including (but not limited to) the following concepts. The strategy below is presented in OVID syntax; the search was simultaneously conducted across Embase, Medline, and PsycINFO. A parallel strategy was used to search the databases comprising the Cochrane Library.

Medical Subject Headings (MeSH), Emtree, PsycINFO and Keywords

Conventions:

OVID

$ = truncation character (wildcard)

exp = "explodes" controlled vocabulary term. E.g. expands search to all more specific related terms in the vocabulary's hierarchy.

.de. = limit controlled vocabulary heading

.fs. = floating subheading

.hw. = limit to heading word

.md. = type of methodology (PsycINFO)

.mp. = combined search fields (default if no fields are specified)

.pt. = publication Type

.ti. = limit to title

.tw. = limit to title and abstract fields

PubMed

[mh] = MeSH heading

[majr] = MeSH heading designated as major topic

[pt] = Publication Type

[sb] = Subset of PubMed database (PreMedline, Systematic, OldMedline)

[sh] = MeSH subheading (qualifiers used in conjunction with MeSH headings)

[tiab] = keyword in title or abstract

[tw] = Text word

Topic-specific Search Terms

Direct Crash Risk

Accident
Accident prevention
Accidents
Accidents, occupational
Accidents, traffic
Automobile driver examination
Automobile driving
Automobiles
Bus
Buses
Car
Car driving
Cars
Collision$
Crash$
Drive$
Driver$
Driver license
Drivers
Driving$
Driving ability
Driving behavior
Haul
Highway
Highway safety
Licens$
Licensure
Long distance
Lorry
Lorries

Motor$
Motor traffic accidents
Motor vehicle
Motor vehicles
Occupational accident
safety
Semi-trailer$
Ticket$
Traffic accident
Traffic safety
Transportation accidents
Truck$1
Vehicle$
Wreck$

Neurocognitive Function

Aware
exp Cognition/
Continuous performance test
Divided attention task
Eye movement
exp Mental function/
exp Mental processes/
exp Neuropsychological performance/
exp Perceptual motor processes/
exp Performance/
Psychomotor
exp Psychomotor performance/
exp Reaction time/
exp Response latency/
Road tracking test
Unaware

Kidney disease

Blood urea nitrogen

Chronic renal

Chronic kidney

Glomerular filtration rate

Exp kidney disease/

Exp kidney diseases/

Exp kidney failure/

Kidney failure

Kidney function

Exp kidney failure chronic/

Renal failure

Renal function

Radioisotope renography

Renography

Urea nitrogen blood level

Sleep

Sleep$

Somnolence

Table 52. CINAHL/Embase/Medline/PsycINFO search concepts, statements, and numbers identified for kidney disease

Set Number	Concept	Search statement	#Identified
1	Kidney disease	Exp kidney failure/ or exp kidney failure chronic/ or exp kidney diseases/ or exp kidney disease/	385029
2		((renal$ or kidney$) adj (chronic$ or failure$))	152741
3		(Blood urea nitrogen or urea nitrogen blood level or glomerular filtration rate or radioisotope renography or renography).de.	22154
4		(kidney or renal) adj function	71390
5	Combine sets	or/1-4	437363
6	Cognition	5 and (exp mental processes/ or exp psychomotor/ or exp neuropsychological performance or exp performance/ or exp reaction time/ or exp mental function/ or exp response latency/ or exp cognition/ or exp perceptual motor processes/ or exp psychomotor performance/)	10070
7	Attention	5 and (Aware or continuous performance test or road tracking test or divided attention task or eye movement or unaware)	1924
8	Accidents	5 and (accident or accidents or accidents, traffic or traffic accident or motor traffic accidents or accidents, occupational or accident prevention or occupational accident or transportation accidents).de.	502
9		5 and ((accident$ and (motor or traffic)) or collision$ or crash$ or wreck$ or citation$ or ticket$)	609
10	Driving	5 and (Automobiles or Motor vehicles or Motor vehicle or Automobile driving or Car driving or Driving ability or Driving behavior or Drivers).de.	43
11		5 and (driver$ or driving$ or drive or licens$ or higway$ or car or cars or motor$ or vehicle$ or semi-trailer$ or bus or buses or truck$1 or lorry or lorries or haul or (long adj distance)).ti.	189
12		5 and (Automobile driver examination or Licensure or Driver license or Safety or Traffic safety or Highway safety or Occupational safety or Occupational Health or Occupational disease).de.	1693
13		5 and (sleep$ or somnolence)	2508
14	Combine sets	or/6-13	15364
15	Limit by population	14 and (exp child/ or adolescent.de. or child$ or pediatr$ or paediatr$ or juvenile$ or adolescen$ or teen$ or youth$)	2878
16		15 and adult	1239

Set Number	Concept	Search statement	#Identified
17		15 not 16	1639
18		14 not 17	13725
19	Limit by publication type	18 not ((letter or editorial or news or comment or case reports or note or conference paper).de. or (letter or editorial or news or comment or case reports).pt.)	11533
20	Limit by study type	19 and ((Randomized controlled trials or random allocation or double-blind method or single-blind method or placebos or cross-over studies or crossover procedure or double blind procedure or single blind procedure or placebos or latin square design or crossover design or double-blind studies or single-blind studies or triple-blind studies or random assignment or exp controlled study/ or exp clinical trial/ or exp comparative study/ or cohort analysis or follow-up studies.de. or intermethod comparison or parallel design or control group or prospective study or retrospective study or case control study or major clinical study).de. or Case control studies/ or Cohort/ or Longitudinal studies/ or Evaluation studies/ or Follow-up studies/ or Prospective studies/ or Retrospective studies/ or Case control study/ or Cohort analysis/ or Longitudinal study/ or Follow up/ or Cohort analysis/ or Followup studies/ or random$.hw. or random$.ti. or placebo$.mp. or ((singl$ or doubl$ or tripl$ or trebl$) and (dummy or blind or sham or mask)).mp. or latin square.mp. or (time adj series) or (case adj (study or studies) or ISRCTN$.mp. or ACTRN$.mp. or (NCT$ not nctc$)))	6113
21	Eliminate overlap	Remove duplicates from 20	5854

English language, human

Dialysis

The search strategies employed combinations of freetext keywords as well as controlled vocabulary terms including (but not limited to) the following concepts. The strategy below is presented in OVID syntax; the search was simultaneously conducted across Embase, Medline, and PsycINFO. A parallel strategy was used to search the databases comprising the Cochrane Library.

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[tiab] = keyword in title or abstract

[tw] = Text word

Topic-specific Search Terms

Dialysis

exp Dialysis
Dialysis
Hemodialy$
Haemodialy$
exp Hemodialysis
exp Peritoneal dialysis
exp Renal dialysis
Renal replacement therapy

Direct Crash Risk

Accident
Accident prevention
Accidents
Accidents, occupational
Accidents, traffic
Automobile driver examination
Automobile driving
Automobiles
Bus
Buses
Car
Car driving
Cars
Collision$
Crash$
Drive$
Driver$
Driver license
Drivers
Driving$

Driving ability
Driving behavior
Haul
Highway
Highway safety
Licens$
Licensure
Long distance
Lorry
Lorries
Motor$
Motor traffic accidents
Motor vehicle
Motor vehicles
Occupational accident
safety
Semi-trailer$
Ticket$
Traffic accident
Traffic safety
Transportation accidents
Truck$1
Vehicle$
Wreck$

Neurocognitive Function

Aware
exp Cognition/
Continuous performance test
Divided attention task
Eye movement
exp Mental function/
exp Mental processes/

exp Neuropsychological performance/

exp Perceptual motor processes/

exp Performance/

Psychomotor

exp Psychomotor performance/

exp Reaction time/

exp Response latency/

Road tracking test

Unaware

Sleep-related

Sleep$

Somnolence

Table 53. CINAHL/Embase/Medline/PsycINFO Search Concepts, Statements, and Number of Publications Identified on Dialysis

Set Number	Concept	Search statement	#Identified
1	Dialysis	Exp renal dialysis/ or exp peritoneal dialysis/ or exp dialysis/ or exp hemodialysis/	111436
2		Dialysis or hemodialy$ or haemodialy$ or renal replacement therapy	137376
3	Combine sets	1 or 2	140152
4	Cognition	3 and (exp mental processes/ or exp psychomotor/ or exp neuropsychological performance or exp performance/ or exp reaction time/ or exp mental function/ or exp response latency/ or exp cognition/ or exp perceptual motor processes/ or exp psychomotor performance/)	3665
5	Attention	3 and (Aware or continuous performance test or road tracking test or divided attention task or eye movement or unaware)	544
6	Accidents	3 and (accident or accidents or accidents, traffic or traffic accident or motor traffic accidents or accidents, occupational or accident prevention or occupational accident or transportation accidents).de.	127
7		3 and ((accident$ and (motor or traffic)) or collision$ or crash$ or wreck$ or citation$ or ticket$)	142
8	Driving	3 and (Automobiles or Motor vehicles or Motor vehicle or Automobile driving or Car driving or Driving ability or Driving behavior or Drivers).de.	13
9		3 and (driver$ or driving$ or drive or licens$ or highway$ or car or cars or motor$ or vehicle$ or semi-trailer$ or bus or buses or truck$1 or lorry or lorries or haul or (long adj distance)).ti.	89
10		3 and (Automobile driver examination or Licensure or Driver license or Safety or Traffic safety or Highway safety or Occupational safety or Occupational Health or Occupational disease).de.	633
11		3 and (sleep$ or somnolence)	801
12	Combine sets	or/4-11	5589
13	Limit by population	12 and (exp child/ or adolescent.de. or child$ or pediatr$ or paediatr$ or juvenile$ or adolescen$ or teen$ or youth$)	775
14		13 and adult	396
15		13 not 14	379
16		12 not 15	5210

Set Number	Concept	Search statement	#Identified
17	Limit by publication type	18 not ((letter or editorial or news or comment or case reports or note or conference paper).de. or (letter or editorial or news or comment or case reports).pt.)	4400
18	Limit by study type	19 and ((Randomized controlled trials or random allocation or double-blind method or single-blind method or placebos or cross-over studies or crossover procedure or double blind procedure or single blind procedure or placebos or latin square design or crossover design or double-blind studies or single-blind studies or triple-blind studies or random assignment or exp controlled study/ or exp clinical trial/ or exp comparative study/ or cohort analysis or follow-up studies.de. or intermethod comparison or parallel design or control group or prospective study or retrospective study or case control study or major clinical study).de. or Case control studies/ or Cohort/ or Longitudinal studies/ or Evaluation studies/ or Follow-up studies/ or Prospective studies/ or Retrospective studies/ or Case control study/ or Cohort analysis/ or Longitudinal study/ or Follow up/ or Cohort analysis/ or Followup studies/ or random$.hw. or random$.ti. or placebo$.mp. or ((singl$ or doubl$ or tripl$ or trebl$) and (dummy or blind or sham or mask)).mp. or latin square.mp. or (time adj series) or (case adj (study or studies) or ISRCTN$.mp. or ACTRN$.mp. or (NCT$ not nctc$)))	1913
19	Eliminate overlap	Remove duplicates from 20	1776

The search strategies employed combinations of freetext keywords as well as controlled vocabulary terms including (but not limited to) the following concepts. The strategy below is presented in OVID syntax; the search was simultaneously conducted across Embase, Medline, and PsycINFO. A parallel strategy was used to search the databases comprising the Cochrane Library.

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[tw] = Text word

Topic-specific Search Terms

Direct Crash Risk

Accident
Accident prevention
Accidents
Accidents, occupational
Accidents, traffic
Automobile driver examination
Automobile driving
Automobiles
Bus
Buses
Car
Car driving
Cars
Collision$
Crash$
Drive$
Driver$
Driver license
Drivers
Driving$
Driving ability
Driving behavior
Haul
Highway
Highway safety
Licens$
Licensure
Long distance
Lorry

Lorries
Motor$
Motor traffic accidents
Motor vehicle
Motor vehicles
Occupational accident
safety
Semi-trailer$
Ticket$
Traffic accident
Traffic safety
Transportation accidents
Truck$1
Vehicle$
Wreck$

Kidney Transplantation

exp Immunosuppressive agent/

exp Immunosuppressive agents/

exp Kidney transplantation

Kidney$/transplantation

Kidney transplant$

Kidney transplant$

Neurocognitive Function

Aware
exp Cognition/
Continuous performance test
Divided attention task
Eye movement
exp Mental function/

exp Mental processes/
exp Neuropsychological performance/
exp Perceptual motor processes/
exp Performance/
Psychomotor
exp Psychomotor performance/
exp Reaction time/
exp Response latency/
Road tracking test
Unaware

Sleep-related

Sleep$
Somnolence

CINAHL/Embase/Medline/PsycINFO Search Concepts, Statements, and Number of Publications Identified for Kidney transplantation

Set Number	Concept	Search statement	#Identified
1	Kidney transplantation	Exp kidney transplantation or ((renal or kidney) adj2 transplant$) or kidney$/tr	96155
2	Immuno-suppressive drugs	Exp immunosuppressive agent/ or exp immunosuppressive agents/	310917
3	Adverse effects	2 and (ae or de or co or si).fs.	154574
4	Combine sets	1 or 3	231317
5	Cognition	4 and (exp mental processes/ or exp psychomotor/ or exp neuropsychological performance or exp performance/ or exp reaction time/ or exp mental function/ or exp response latency/ or exp cognition/ or exp perceptual motor processes/ or exp psychomotor performance/)	6111
6	Attention	4 and (Aware or continuous performance test or road tracking test or divided attention task or eye movement or unaware)	1243
7	Accidents	4 and (accident or accidents or accidents, traffic or traffic accident or motor traffic accidents or accidents, occupational or accident prevention or occupational accident or transportation accidents).de.	139
8		4 and ((accident$ and (motor or traffic)) or collision$ or crash$ or wreck$ or citation$ or ticket$)	245
9	Driving	4 and (Automobiles or Motor vehicles or Motor vehicle or Automobile driving or Car driving or Driving ability or Driving behavior or Drivers).de.	13
10		4 and (driver$ or driving$ or drive or licens$ or higway$ or car or cars or motor$ or vehicle$ or semi-trailer$ or bus or buses or truck$1 or lorry or lorries or haul or (long adj distance)).ti.	180
11		4 and (Automobile driver examination or Licensure or Driver license or Safety or Traffic safety or Highway safety or Occupational safety or Occupational Health or Occupational disease).de.	1155
12		4 and (sleep$ or somnolence)	464
13	Combine sets	or/5-12	9279
14	Limit by population	13 and (exp child/ or adolescent.de. or child$ or pediatr$ or paediatr$ or juvenile$ or adolescen$ or teen$ or youth$)	1885
15		14 and adult	793
16		14 not 15	1092

Set Number	Concept	Search statement	#Identified
17		13 not 16	8187
18	Limit by publication type	17 not ((letter or editorial or news or comment or case reports or note or conference paper).de. or (letter or editorial or news or comment or case reports).pt.)	6997
19	Limit by study type	18 and ((Randomized controlled trials or random allocation or double-blind method or single-blind method or placebos or cross-over studies or crossover procedure or double blind procedure or single blind procedure or placebos or latin square design or crossover design or double-blind studies or single-blind studies or triple-blind studies or random assignment or exp controlled study/ or exp clinical trial/ or exp comparative study/ or cohort analysis or follow-up studies.de. or intermethod comparison or parallel design or control group or prospective study or retrospective study or case control study or major clinical study).de. or Case control studies/ or Cohort/ or Longitudinal studies/ or Evaluation studies/ or Follow-up studies/ or Prospective studies/ or Retrospective studies/ or Case control study/ or Cohort analysis/ or Longitudinal study/ or Follow up/ or Cohort analysis/ or Followup studies/ or random$.hw. or random$.ti. or placebo$.mp. or ((singl$ or doubl$ or tripl$ or trebl$) and (dummy or blind or sham or mask)).mp. or latin square.mp. or (time adj series) or (case adj (study or studies) or ISRCTN$.mp. or ACTRN$.mp. or (NCT$ not nctc$)))	4113
20	Eliminate overlap	Remove duplicates from 19	4005

Appendix B: Retrieval Criteria

Listed below are the retrieval critera, the criteria that each identified abstract had to satisfy in order to be retrieved in full.

Retrieval Criteria for Key Question 1

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Article must describe a study that attempted to determine the risk for a motor vehicle crash directly (risk for a fatal or nonfatal crash) associated with kidney disease.
    - Reporting direct evidence of crash risk
    - Reporting neurocognitive function outcomes associated with increased risk of crash
    - Reporting sleep-related outcomes associated with increased risk of crash
- Article must describe a study that includes a comparison group comprised of comparable subjects who do not have kidney disease.

Retrieval Criteria for Key Question 2

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Article must describe a study that attempted to determine the risk for a motor vehicle crash directly (risk for a fatal or nonfatal crash) associated with kidney disease in patients taking medications.
    - Reporting direct evidence of crash risk
    - Reporting neurocognitive function outcomes associated with increased risk of crash
    - Reporting sleep-related outcomes associated with increased risk of crash
- Article must describe a study that includes a comparison group comprised of comparable subjects who do not have kidney disease and are not taking those medications.

Retrieval Criteria for Key Question 3

- Article must have been published in the English language.

- Article must have enrolled 10 or more subjects.
- Article must describe a study that attempted to determine the risk for a motor vehicle crash directly (risk for a fatal or nonfatal crash) associated with kidney disease in patients on peritoneal dialysis or hemodialysis.
    - Reporting direct evidence of crash risk
    - Reporting neurocognitive function outcomes associated with increased risk of crash
    - Reporting sleep-related outcomes associated with increased risk of crash
- Article must describe a study that includes a comparison group comprised of comparable subjects who do not have kidney disease and are not being treated with peritoneal dialysis or hemodialysis.

Retrieval Criteria for Key Question 4

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Article must describe a study that attempted to determine the risk for a motor vehicle crash directly (risk for a fatal or nonfatal crash) associated with kidney transplant to treat kidney disease.
    - Reporting direct evidence of crash risk
    - Reporting neurocognitive function outcomes associated with increased risk of crash
    - Reporting sleep-related outcomes associated with increased risk of crash
- Article must describe a study that includes a comparison group comprised of comparable subjects who do not have kidney disease and have not had a kidney transplant.

Appendix C: Inclusion Criteria

Listed below are the inclusion criteria for each of the four key questions addressed in this evidence report. These are the criteria that had to be satisfied in order for an article to be included in the evidence base.

Inclusion Criteria for All Key Questions

- Article must have been published in the English language.
- Article must be a full-length article. Abstracts and letters to the editor will not meet this inclusion criterion.
- Article must have enrolled 10 or more subjects per group
- Article must describe a study that attempted to determine the risk for a motor vehicle crash associated with kidney disease.
    - Article must compare the proportion of drivers with kidney disease who crashed (cases) with the proportion of comparable individuals without the disorder who did not crash (controls).
    - Article must compare the proportion of individuals with kidney disease among a group of drivers who crashed (cases) with the proportion of individuals with kidney disease among a comparable group of individuals who did not crash (controls).
- Article may describe a study that attempted to evaluate the relationship between kidney disease and the following direct and indirect measures of driver safety:
    - Measures of driving-related performance (laboratory and experimental)
    - Measures of driving-related cognitive function
    - Measures of driving-related psychomotor function
    - Measures of driving-related sleepiness or sleep dysfunction
- Article must present data in a manner that will allow ECRI Institute to calculate (directly or through imputation) effect-size estimates and confidence intervals.

Additional Criterion for Key Question 2

- Study subjects must have been taking medications for treatment of kidney disease or related effects, and controls must not have kidney disease or be taking the medication(s) in question.

Additional Criterion for Key Question 3

- Study subjects must be undergoing hemodialysis or peritoneal dialysis treatment for kidney disease, and controls must not be.

Additional Criterion for Key Question 4

- Study subjects must have undergone kidney transplant as treatment for kidney disease, and controls must not have.

Appendix D: Excluded Articles

Table D-1. Excluded studies (Key Question 1)

Reference	Year	Reason for Exclusion
Direct Crash Evidence		
Dischinger et al.(41)	2000	Diagnosis of drivers reported on, "genitourinary disorder," includes persons without kidney disease
Lyman et al.(143)	2001	Does not report on crash
Stewart et al.(144)	1993	Number of patients with kidney disease (or proteinuria) not reported
Neurocognitive Evidence		
Altmann et al.(145)	1989	Treatment outdated and therefore not relevant. Studies effects of aluminum on cerebral function; Aluminum is no longer used (See USRDS Atlas)
Ginn et al.(146)	1975	Does not report on functional impairment
Lindsay et al.(147)	2006	Does not report on functional impairment
Lyman et al.(143)	2001	Does not report on functional impairment
Ogunrin et al.(148)	2006	Data not fully reported: means and measures of variance not reported
Sithinamsuwan et al.(149)	2005	Does not report on functional impairment
Sleep-related Evidence		
Kuhlman et al.(80)	2000	Not an experimental or comparative clinical study (a prevalence study)
Markou et al.(150)	2006	Not an experimental or comparative clinical study (a prevalence study)
Parker et al.(151)	2003	Not an experimental or comparative clinical study (a prevalence study)
Perl et al.(67)	2006	Not an experimental or comparative clinical study (a literature review)
Rodrigues et al.(152)	2005	Not an experimental or comparative clinical study (a prevalence study)
Stepanski et al.(68)	1995	Not an experimental or comparative clinical study (a prevalence study)
Unruh et al.(81)	2006	Not an experimental or comparative clinical study (identifies correlates with sleep quality at one time point in a single cohort)
Wadhwa et al.(153)	1992	Not an experimental or comparative clinical study (a prevalence study)

Table D-2. Excluded studies (Key Question 2)

Reference	Year	Reason for Exclusion
Direct Crash Evidence		
Delaney et al.(101)	2005	Subjects not diagnosed with kidney disease
Lindberg et al. 2001(27)	2001	No outcomes on driving reported
McGwin et al.(102)	2000	Subjects not diagnosed with kidney disease
Verseter et al.(100)	2003	Subjects not diagnosed with kidney disease
Verster et al.(154)	2003	Subjects not diagnosed with kidney disease
Vuurman et al.(98)	2004	Subjects not diagnosed with kidney disease
Neurocognitive Evidence		
Lindberg et al. 2001(27)	2001	No outcomes on neurocognitive impairment reported
Sleep-related Evidence		
Kuhlman et al.(80)	2000	Not an experimental or comparative clinical study (a prevalence study)
Markou et al.(150)	2006	Not an experimental or comparative clinical study (a prevalence study)
Parker et al.(151)	2003	Not an experimental or comparative clinical study (a prevalence study)
Perl et al.(67)	2006	Not an experimental or comparative clinical study (a literature review)
Rodrigues et al.(152)	2005	Not an experimental or comparative clinical study (a prevalence study)
Stepanski et al.(68)	1995	Not an experimental or comparative clinical study (a prevalence study)
Unruh et al.(81)	2006	Not an experimental or comparative clinical study (identifies correlates with sleep quality at one time point in a single cohort)
Wadhwa et al.(153)	1992	Not an experimental or comparative clinical study (a prevalence study)

Table D-3. Excluded studies (Key Question 3)

Reference	Year	Reason for Exclusion
Direct Crash Evidence		
Dischinger et al.(41)	2000	Diagnosis of drivers reported on, "genitourinary disorder," includes persons without kidney disease
Lyman et al.(143)	2001	Does not report on crash
Stewart et al.(144)	1993	Number of patients with kidney disease (or proteinuria) not reported
Neurocognitive Evidence		
Altmann et al.(145)	1989	Treatment outdated and therefore not relevant. Studies effects of aluminum on cerebral function; Aluminum is no longer used (See USRDS Atlas)
Ginn et al.(146)	1975	Does not report on functional impairment
Lee et al.(155)	2004	No measure of variance reported
Lindsay et al.(147)	2006	Does not report on functional impairment
Lyman et al.(143)	2001	Does not report on functional impairment
McKee et al.(156)	1982	Insufficient control: cohorts assessed at time one and time 2 were different, unmatched patient groups
Ogunrin et al.(148)	2006	Data not fully reported: means and measures of variance not reported
Sithinamsuwan et al.(149)	2005	Does not report on functional impairment
Smith and Winslow(157)	1990	Reported time points statistically incompatible with those from the other studies
Temple et al.(158)	1995	Fewer than 10 patients per group
Temple et al.(159)	1992	Fewer than 10 patients per group
Thornton et al.(123)	2007	Patients not treated with dialysis
Sleep-related Evidence		
Kuhlman et al.(80)	2000	Not an experimental or comparative clinical study (a prevalence study)
Markou et al.(150)	2006	Not an experimental or comparative clinical study (a prevalence study)
Parker et al.(151)	2003	Not an experimental or comparative clinical study (a prevalence study)
Perl et al.(67)	2006	Not an experimental or comparative clinical study (a literature review)
Rodrigues et al.(152)	2005	Not an experimental or comparative clinical study (a prevalence study)
Stepanski et al.(68)	1995	Not an experimental or comparative clinical study (a prevalence study)
Unruh et al.(81)	2006	Not an experimental or comparative clinical study (identifies correlates with sleep quality at one time point in a single cohort)
Venmans et al.(160)	1995	Insufficient number of patients. Post data was reported for only 9 patients (60% of enrolled population).
Wadhwa et al.(153)	1992	Not an experimental or comparative clinical study (a prevalence study)

Table D-4. Excluded studies (Key Question 4)

Study	Year	Reason for exclusion
Neurocognitive Evidence		
Wolkowitz et al.(161)	1990	Subjects not diagnosed with kidney disease
Sleep-related Evidence		
Kuhlman et al.(80)	2000	Not an experimental or comparative clinical study (a prevalence study)
Perl et al.(67)	2006	Not an experimental or comparative clinical study (a literature review)

Appendix E: Determining the Strength and Stability of a Body of Evidence

As stated in the main text, ECRI Institute evidence reports differ substantially from other systematic review in that we provide two types of conclusion; qualitative conclusions and quantitative conclusions. In order to reach these conclusions we use an algorithm developed by ECRI Institute to guide the conduct and interpretation of the analyses performed during the development of this evidence report.(112) The algorithm, which is presented in Figure E-1 through Figure E-4, formalizes the process of systematic review by breaking the process down into several discrete steps. At each step, rules are applied that determine the next step in the systematic review process and ultimately to the stability and strength of evidence ratings that are allocated to our conclusions. Because the application of the rules governing each step in the algorithm (henceforth called a decision point) guide the conduct of the systematic review process and how its findings are interpreted, much time and effort was spent in ensuring that the rules and underlying assumptions for each decision point were reasonable.

The algorithm is comprised of three distinct sections: a *General* section, a *Quantitative* section, and a *Qualitative* section. Each of these sections, the decision points that fall within them, and the decision rules that were applied at each step in the present evidence report are described below.

Decision Point 1: Acceptable Quality?

Decision Point 1 serves two purposes: 1) to assess the quality of each included study; 2) to provide a means of excluding studies that are so prone to bias that their reported results cannot be considered useful. To aid in assessing the quality of each of the studies included in this evidence report, we used two study quality assessment instruments. The choice of which instrument to use was based on the design of the study used to address the key questions of interest. In this evidence report we used the ECRI Institute Quality Scale I (for randomized and non-randomized comparative studies), the ECRI Institute Quality Scale III (for pre-post studies) and revised versions of the Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies(162) and Newcastle-Ottawa Quality Assessment Scale for Cohort Studies. These instruments are presented in Appendix F.

Decision Point 2: Is Quality of Evidence Base Acceptable?

We classified the overall quality of each key question specific evidence base into one of three distinct categories; high, moderate or low quality. Decisions about the quality of each evidence base were based on data obtained using the quality assessment instruments described above using the criteria presented in Table E-1.

Table E-1. Criteria Used to Categorize Quality of Evidence Base

Quality Category	Median Score			
	ECRI Instrument for Comparative Studies	ECRI Instrument for Pre-Post Studies	Newcastle-Ottawa Scale for Case-Control Studies	Newcastle-Ottawa Scale for Cohort Studies
High Quality	≥9.0			
Moderate Quality	6.0 to 8.9	≥9.0	≥8.0	≥8.0
Low Quality	≤6.0	<9.0	<8.0	<8.0

Decision Point 3: Quantitative Analysis Performed?

In this evidence report, deciding whether to combine study findings in meta-analysis depended on a number of important factors, including:

- The number of available studies for each outcome
    - For any outcome, combinable data from at least 3 studies must be available before a quantitative analysis will be considered. This factor frequently that prevented quantitative analysis in the evidence bases in this report.
- The clinical heterogeneity among studies in terms of patient populations and details of treatments and related medical care given
    - Kidney disease ranges in spectrum from mild to life-threatening. In Key Question 1, the inclusion of patients with kidney disease of any degree resulted in evidence bases with mixed populations.
- The methodological heterogeneity among studies in terms of study design type and basis of comparison
    - Studies included in this report had prospective or retrospective cohort-controlled, historically-controlled cohort, pre-post, and randomized controlled trial designs. Some of these studies cannot be combined in a quantitative analysis. Others can be technically combined, but the impact of the different study designs would be unclear, given the small size of all of the evidence bases and consequent small power to detect substantial differences between study designs in sensitivity analyses.
- The adequacy of reporting of study findings for each included study in a given evidence base
    - In some cases, studies reported the same outcome in different ways that are not statistically compatible, such as some studies dichotomizing continuous outcomes and others not.

If 4 or more studies were available but any of the above limitations precluded ECRI Institute from directly computing relevant effect size estimates for >75 percent of the available studies, no quantitative analysis were performed. If no quantitative analyses were performed, we moved directly to Decision Point 8 which deals with the assessment of the available evidence with the aim of drawing a purely qualitative conclusion.

Decision Point 4: Are Data Quantitatively Consistent (Homogeneous)?

This decision point was used only when the answer to Decision Point 3 was affirmative and a quantitative analysis was performed. Quantitative consistency refers to the extent to which the quantitative results of different studies are in agreement. As limitations in the evidence base prevented us from performing quantitative analyses, this decision point is not relevant to this report so we will discuss it no further.

Decision Point 5: Are Findings Stable (Quantitatively Robust)?

If the findings of the fixed-effects meta-analysis were found to be informative, we next assessed the stability of the summary effect size estimate obtained. As this was never this case in this evidence report, we will discuss it no further.

Decision Points 6 and 7: Exploration of Heterogeneity

We always attempt to determine the source of heterogeneity when the evidence base consists of 10. In preparing this evidence report we did not encounter any such situations. Consequently, Decision Points 6 and 7 are irrelevant to the present report and we do not discuss them further.

Decision Point 8: Are Qualitative Findings Robust?

Decision Point 8 allows one to determine whether the qualitative findings of two or more studies can be overturned by sensitivity analysis. For this evidence report, a single sensitivity analysis was performed–a random-effects cumulative meta-analysis (cREMA). We considered our qualitative findings to be overturned only when the findings of the cREMA altered our qualitative conclusion (i.e., a statistically significant finding became non-significant as studies were added to the evidence base). If the qualitative findings of the last three study additions were in agreement then we concluded that our qualitative findings were robust.

Decision Point 9: Are Data Qualitatively Consistent?

The purpose of this decision point is to determine whether the qualitative findings of an evidence base consisting of only two studies are the same. For example one might ask, “Do both included studies find thatindividuals with kidney disease are at an increased risk for a motor vehicle crash?”

Decision Point 10: Is Magnitude of Treatment Effect Large?

When considering the strength of evidence supporting a qualitative conclusion based on only one or two studies, magnitude of effect becomes very important. The more positive the findings, the more confident one can be that new evidence will not overturn ones qualitative conclusion.

The algorithm divides the magnitude of effect into two categories–large and not large. Determining the threshold above which the observed magnitude of effect can be considered to be "large" cannot usually be determined *a priori*. In cases where it is necessary to make judgments about whether an estimate of treatment effect is extremely large, the project director will present data from the two studies to a committee of three methodologists who will determine whether an effect size estimate is "extremely large" using a modified Delphi technique.

Figure E-1. Quality Assessment and Placement into Quality Tier of System

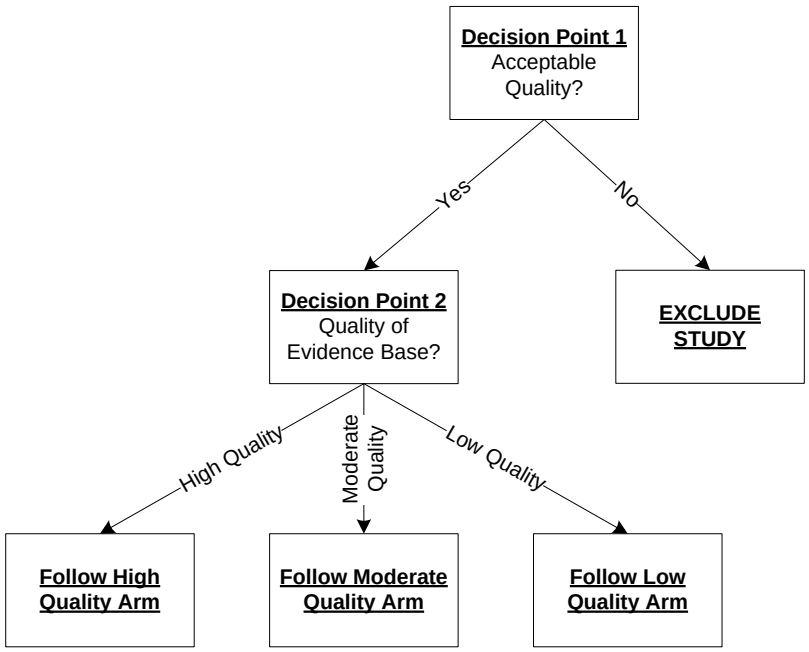


Figure E-2. High Quality Pathway

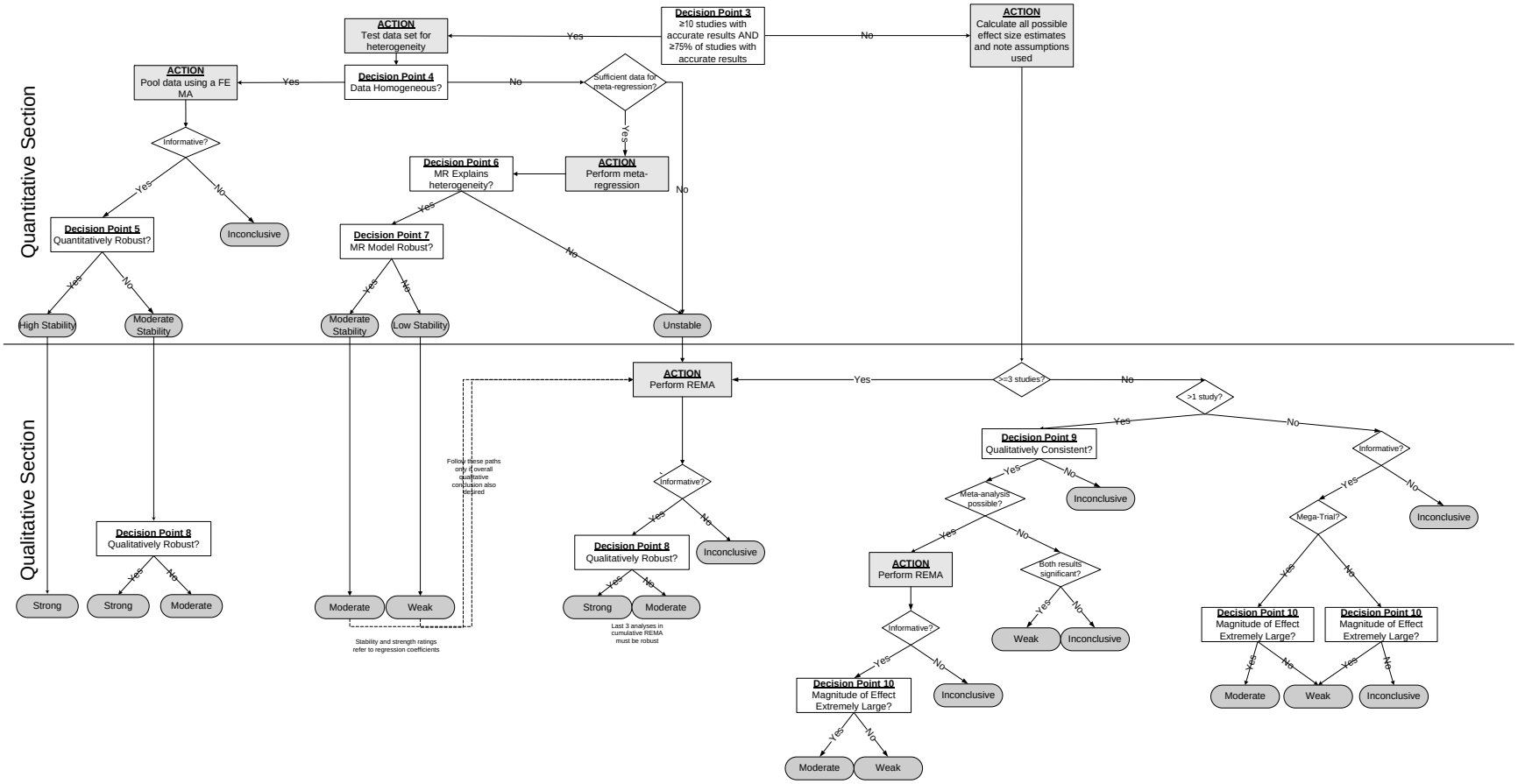


Figure E-3. Moderate Quality Pathway

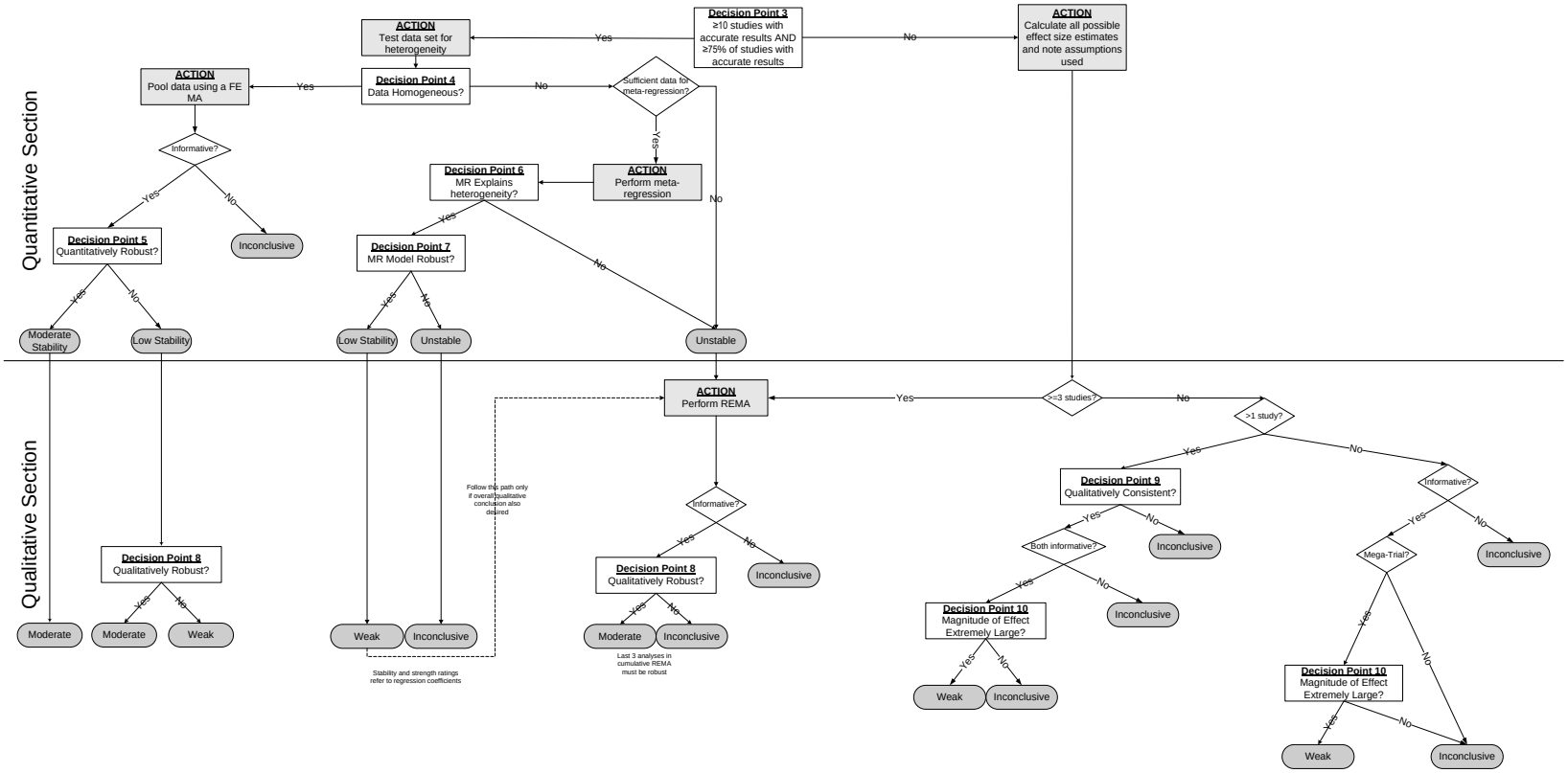
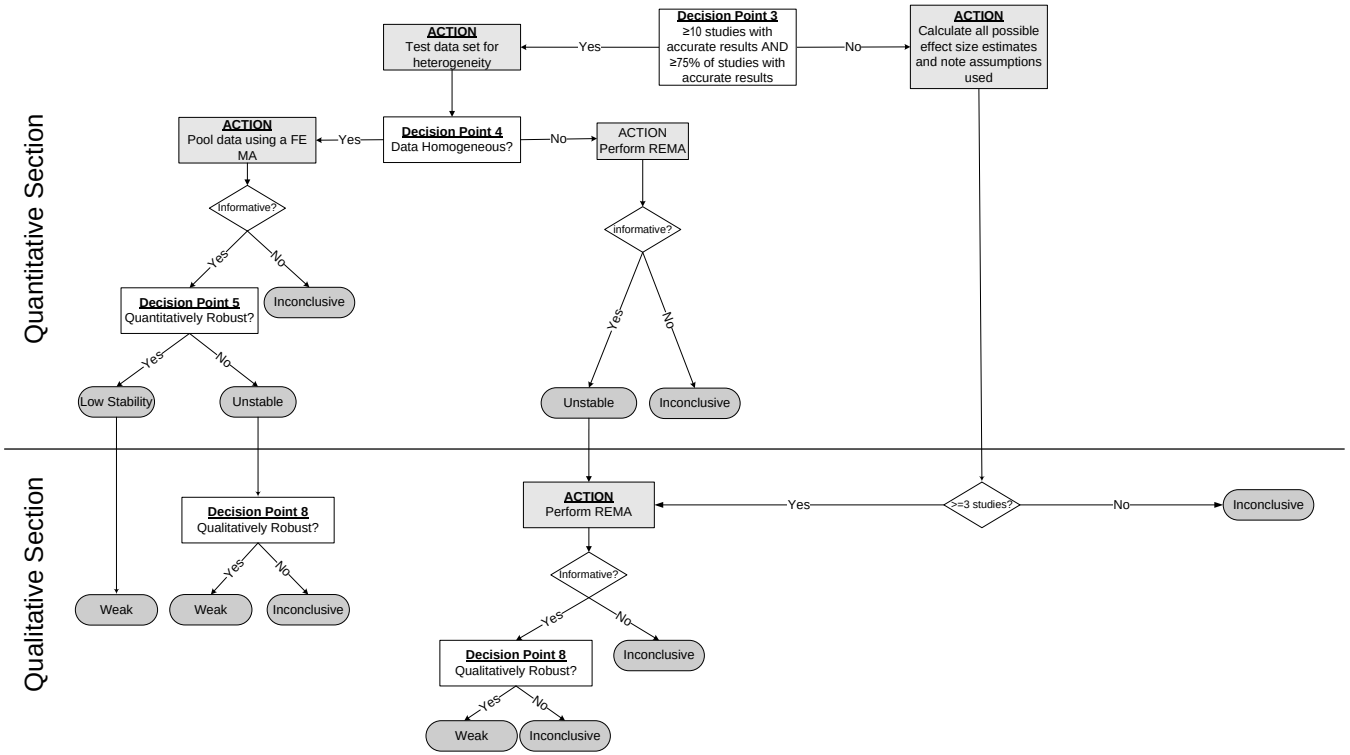


Figure E-4. Low Quality Pathway



Appendix F: Quality Assessment Instruments Used

Three different assessment instruments were used to assess the quality of the studies included in the evidence bases for the key questions addressed in this evidence report; ECRI Institute Quality Scale I for comparative trials, ECRI Institute Quality Scale III for pre-post, and revised version of the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies.

ECRI Institute Quality Scale I: Controlled Trials

Question #	Question
1	Were patients randomly assigned to the study's groups?
2	Did the study employ stochastic randomization?
3	Were any methods other than randomization used to make the patients in the study's groups comparable?
4	Were patients assigned to groups based on factors other than patient or physician preference?
5	Were the *characteristics* of patients in the different study groups comparable at the time they were assigned to groups?
6	Did patients in the different study groups have similar levels of performance on ALL of the outcome variables at the time they were assigned to groups?
7	Was the comparison of interest prospectively planned?
8	Did ≥85% of the patients complete the study?
9	Was there a ≤15% difference in completion rates in the study's groups?
10	Were all of the study's groups concurrently treated?
11	Was compliance with treatment ≥85% in both of the study's groups?
12	Were all of the study's groups treated at the same center?
13	Were subjects blinded to the treatment they received?
14	Did the authors perform any tests after completing the study to ensure that the integrity of the blinding of patients was maintained throughout the study?
15	Was the treating physician blinded to the groups to which the patients were assigned?
16	Were those who assessed the patient's outcomes blinded to the group to which the patients were assigned?
17	Was there concealment of allocation?
18	Was the outcome measure of interest objective **and** objectively measured?
19	Were the same laboratory tests, clinical findings, psychologic instruments, etc. used to measure the outcomes in all of the study's groups?
20	Was the instrument used to measure the outcome standard?
21	Was the same treatment given to all patients enrolled in the experimental group?
22	Was the same treatment given to all patients enrolled in the control group?
23	Were the follow-up times in all of the study's relevant groups approximately equal?
24	Was the funding for this study derived from a source that does not have a financial interest in its results?
25	Were the author's conclusions, as stated in the abstract **or** the article's discussion section, supported by the data presented in the articles results section?

ECRI Institute Quality Assessment Scale III: Pre-Post Studies

Item	Question
1	Was the study prospective?
2	Did the study enroll all patients or consecutive patients?
3	Were the criteria for including and excluding patients based on objective laboratory and/or clinical findings?
4	Were the patient inclusion/ exclusion criteria established *a priori*?
5	Was the same initial treatment given to all patients enrolled?
6	Did all patients receive the same subsequent treatment(s)?
7	Was the outcome measure objective and objectively measured?
8	Did ≥85% of patients complete the study?
9	Were the characteristics of those who did and did not complete the study compared, and were these characteristics similar?
10	Was the funding for this study derived from a source that does not have a financial interest in its results?
11	Were the author's conclusions, as stated in the abstract or the article's discussion section, supported by the data presented in the article's results section?

Revised Newcastle–Ottawa Quality Assessment Scale for Cohort-Control Studies

Question #	Question
1	Are the exposed cohort representative of the average CMV driver in the community?
2	Are the non-exposed cohorts representative?
3	How was exposure determined – secure record?
4	At the designated start of the study, were the controls free of the outcome of interest?
5	What is the comparability of the cohorts on the basis of design or analysis?
6	How was the outcome assessed?
7	Was follow-up adequate for outcome to occur?
8	Was the follow-up adequate for both exposed and non-exposed cohorts?
9	Was the funding free of financial interest?
10	Were the conclusions supported by the data

Appendix G: Study Summary Tables

Study Summary Tables for Key Question 1

Key Question 1: Direct Crash Evidence

McGwin Jr. G, Sims R, Pulley L, and Roseman J. Relations among chronic medical conditions, medications, and automobile crashes in the elderly: a population-based case-control study. Am J Epidemiol 2000; 152: 424-31											
Key Questions Addressed	1		2		3		4				
	✓										
Research Question	Proportion of at-fault crash drivers who have kidney disease compared with proportion of drivers who did not crash										
Study Design	Retrospective cohort control										
Population	**Inclusion Criteria**	Licensed drivers of Mobile County, Alabama aged 65+years involved in at least one automobile crash between January 1 and December 31, 1996									
	Exclusion Criteria	Individuals who possessed licenses for identification purposes only									
	Study population Characteristics		At-fault drivers involved in crashes		Drivers not involved in crashes		Not-at-fault drivers involved in crashes				
		n	249		454		198				
		Age (yr)	%		%		%				
		65-68	21.3		25.7		39.6				
		69-72	25.4		24.4		23.6				
		73-77	25.8		25.7		23.6				
		78-93	27.5		24.2		13.2				
		Gender	%		%		%				
		Male	49.6		49.1		51.1				
		Female	50.4		51.0		48.9				
		Prior crash involvement									
		No	63.9		79.0		66.5				
		Yes	36.1		21.1		33.5				
	Generalizability to CMV drivers	Unclear									
Methods	Drivers aged 65 years and older were selected from Alabama Department of Public Safety driving records. Of the 39,687 eligible individuals, 1,906 had been involved in at least one automobile crash during 1996. 560 individuals were contacted by phone and asked to participate in the study. In addition to the 447 who agreed to participate, a random sample of 1,900 possible controls was selected from similar driving records. Phone interviews took place between June – December 1997 by interviewers blind to case status. Information collected included demographics, chronic medical conditions, medications, and driving habits. A focal reference date of January 1, 1996 was used. Subjects were asked if they had been diagnosed with kidney disease and the medications currently taking for this condition or any others. Crash involvement from 1991 – 1995 was researched via Alabama DPS records.										
Statistical Methods	Frequency distributions, odds ratios, 95% CI, logistic regression										
Quality Assessment	Internal Validity	1	2	3	4	5	6	7	8	9	10

	Category: Moderate	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes
Relevant Outcomes Assessed	At-fault crash rate										
Results	Percent of at-fault drivers involved in crash and diagnosed with kidney disease was 3.2% (Table G-1). Only individuals with diabetic retinopathy or diabetic neuropathy had fewer at-fault drivers (1.6 and 1.2% respectively). Percent of drivers not involved in crash and diagnosed with kidney disorder was 4.7 (OR = 0.7, 95% CI: 0.3, 1.6). Similar results are found after adjusting for age, gender, ethnicity, and annual mileage (OR = 0.7, 95% CI: 0.3, 1.6). Percent of not-at-fault drivers involved in crash with kidney disease is 6.4% (OR = 0.5, 95% CI: 0.2, 1.2). Not-at-fault drivers involved in crashes were more likely to have heart disease, stroke and arthritis compared with drivers not involved in crashes.										
Authors' Comments	Drivers diagnosed with kidney disease did not have an increased risk of crash involvement.										

Table G-1. Medical Characteristics of At-fault and Not-At-fault Drivers Involved in Crashes vs. Drivers Not Involved in Crashes in Mobile County, AL, Jan–Dec 1997

	% at-fault drivers involved in crashes (*n* = 249)	Drivers not involved in crashes (*n* = 454)					Not-at-fault drivers involved in crashes (*n* = 198)				
		%	OR*,†	95% CI*	OR‡	95% CI	%	OR†	95% CI	OR†,‡	95% CI
High blood pressure	42.9	45.7	0.9	0.6, 1.2	0.9	0.6, 1.3	45.7	0.9	0.6, 1.3	0.9	0.6, 1.4
Heart disease	26.0	20.2	1.4	0.9, 2.0	1.5	1.0, 2.2	24.3	1.1	0.7, 1.7	1.0	0.7, 1.7
Stroke	7.3	4.1	1.8	0.9, 3.7	1.9	1.0, 3.9	6.9	1.1	0.5, 2.3	1.1	0.5, 2.4
Cancer	15.3	13.7	1.1	0.7, 1.8	1.2	0.7, 1.9	13.9	1.1	0.6, 2.0	1.0	0.5, 1.8
Arthritis	48.6	43.3	1.2	0.9, 1.7	1.2	0.9, 1.7	47.4	1.1	0.7, 1.6	1.0	0.7, 1.5
Cataracts	44.6	42.8	1.1	0.8, 1.5	1.0	0.7, 1.5	35.1	1.5	1.0, 2.2	1.1	0.7, 1.8
Glaucoma	6.9	8.9	0.8	0.4, 1.4	0.7	0.4, 1.3	5.2	1.4	0.6, 3.2	1.0	0.4, 2.5
Diabetes	13.6	14.0	1.0	0.6, 1.5	0.9	0.6, 1.5	16.0	0.8	0.5, 1.4	0.9	0.5, 1.5
Kidney disease	3.2	4.7	0.7	0.3, 1.6	0.7	0.3, 1.6	6.4	0.5	0.2, 1.2	0.4	0.2, 1.2
Diabetic retinopathy	1.6	1.5	1.1	0.3, 3.8	1.4	0.3, 4.0	1.1	1.5	0.3, 8.2	1.9	0.3, 10.9
Diabetic neuropathy	1.2	0.6	2.0	0.4, 9.8	2.6	0.5, 13.1	0.5	2.3	0.2, 21.8	2.8	0.3, 28.3

*OR, odds ratio; CI, confidence interval; †, reference is those without condition; ‡, adjusted for age, gender, ethnicity and annual mileage

Ysander L. The Safety of Drivers With Chronic Disease. Brit J Industr Med 1966; 23: 28-36

Key Questions Addressed	1	2	3	4
	✓			

Research Question: Assess relationship of chronic illness and crash

Study Design: Retrospective cohort control

Population

Inclusion Criteria: Individuals licensed to drive private cars or CMVs and listed in the driving license registry of the county of Goteborg and Bohus, in Sweden, up to December 31, 1961 and who were granted a license under special conditions of their chronic disease

Exclusion Criteria: None reported

Study population Characteristics

Variable	Cases	Controls
n	612	612
Gender M/F	521/127	

Group	License Restriction	Avg time to hold restricted license	N (%)
Group 1	Physical defect is unlikely to undergo sudden or uncontrolled progress; license is restricted to periodic re-examination	5.2 yrs	527 (82%)
Group 2	Disease condition was similar to Group 1, however restriction of re-examination has been removed with disease seen as not posing a threat to safe driving	7.3 yrs	58 (9%)
Group 3	License withdrawn or surrendered	5.2 yrs	27 (4%)
Group 4	Required to undergo re-exam but died during study period	5.9 yrs	36 (5%)

Generalizability to CMV drivers: Unclear

Methods: All driving data including accidents and offenses from 10-year period 1952-1961was obtained from the driving license registry. Driving data for Group 4 was removed from the study. In addition to renal disorders, study participants were categorized into the following disease groups: diabetes, cardiovascular disease, sense organs, psychiatric disorders, and other organic (including CNS, blood, and locomotion). Individuals were then subdivided by age and gender. Demographics for drivers with kidney disease are shown in Table G-2. Control population consisted of 612 individuals similar in age and gender with interest in only Group1 and Group 2 drivers. 302/612 (50%) of control group and 296/612 (51%) of diseased group were forwarded a questionnaire discussing driving history including number of annual kilometers driven, type of driving (urban or rural) and time (day/nighttime). Questionnaires were returned by approximately 77% of both study groups. Driving record data was subdivided into crashes, serious driving offenses, and minor offenses. Crash was defined as an incident which resulted in damage to vehicles in which the majority of cases resulted in prosecution and conviction.

Statistical Methods: None required

Quality Assessment

Internal Validity Category: Low	1	2	3	4	5	6	7	8	9	10
	No	Yes	Yes	Yes	No	Yes	Yes	No	No	No

Relevant Outcomes Assessed: Crash

Results	17% of Group 1 included 88 individuals with kidney disease. Group 3 subjects were diagnosed with diabetes, cardiovascular disease, renal disorder, disease of sense organs and CNS. Of the 27 drivers in Group 3, 13 were diabetic. A definite connection between disease and crash involvement was demonstrated by 4 diabetic individuals. In two additional cases (one individual with progressive muscular atrophy and one suffering from psychopathy) the effects of disease were considered as a possible contributor to a crash/offense. If these 6 cases are considered, then about 1% of drivers were affected by disease at the time of crash/offense. Results for mileage/driven are shown in Table G-3. Data show similar annual driving distance in both study groups. Number of drivers involved in crash/offense is shown in Table G-4. The control group was involved in more crashes/offenses than the investigation group. Individuals involved in more than one crash/offense were also higher in the control group (18 vs 9). Percentage of drivers involved in crash/offense by diagnostic group is shown in Table G-5. 120 drivers were diagnosed with kidney disease. Of this disease category, only 2.5%of drivers were involved in crashes and 7.5% in crash/offense. Results again show a higher percent of the control group with frequency of crash and serious driving offense versus the chronic disease group (15.3% vs 9.8%).
Authors' Comments	Only 1% of the 612 drivers with chronic disease were affected by disease at the time of crash/serious driving offense. None of the affected individuals were diagnosed with kidney disease.

Table G-2. Drivers in Group 1 with Kidney disease

AGE GROUPS OF DRIVERS IN GROUP 1 WITH RENAL DISEASE

Diagnostic Group	*Age Group*							*Total*
	18-20	*21-25*	*26-30*	*31-40*	*41-50*	*51-60*	*> 60*	
Nephropathy with hypertension				5	4			9
Nephropathy without hypertension	2	9	5	6	4	1	2	29
Nephropathy with proteinuria only	7	4	4	9	5	1	1	31
Orthostatic albuminuria	7	7	5					19
Total	16	20	14	20	13	2	3	88

Table G-3. Annual Driving Distance by Age Group

INVESTIGATION (I) AND CONTROL (C) SERIES

Stated Annual Distance Driven (km.)	*Age Group*					
	18-25		*26-50*		*> 50*	
	I	*C*	*I*	*C*	*I*	*C*
0	0	2	3	5	1	6
1-4,999	20	20	23	25	9	5
5,000-9,999	17	18	31	29	15	12
10,000-19,999	25	25	46	42	6	17
20,000 and above	17	8	13	16	1	3
	(33,500)*	(31,750)	(29,000)	(32,600)	(25,000)	(38,300)

*The figures in brackets give the average number of km./year for drivers who reported distances of 20,000 km./year or more

Number of drivers with equal annual driving distance in different age groups in the investigation (I) and control (C) series.

Table G-4. Driver Involvement in Crash/Serious Driving Offense

No. of Drivers Involved In		*Age Group*							*Total*
		18-20	*21-25*	*26-30*	*31-40*	*41-50*	*51-60*	*> 60*	
Road accidents	I	0	4	1	5	6	4	5	25
	C	0	12	11	13	4	6	1	47
Serious driving offences	I	2	7	6	8	5	7	0	35
	C	1	11	6	11	12	4	2	47

Numbers of drivers involved in crashes or serious driving offenses in the investigation (I) and Control (C) series, according to age groups

Table G-5. Percentage of Drivers Involved in Crash/Offense by Disease Category

Investigation or Diagnostic Group	*Drivers with Road Accidents (%)*	*Drivers with Road Accidents and Serious Driving Offences (%)*
Whole investigation series except Group 4 m = 4·5 n = 612	4·1	9·8
Group 1 m = 4·6 n = 527	3·4	9·3
Group 2 m = 4·9 n = 58	1·7	3·4
Group 3 m = 4·1 n = 27	22·2	29·6
Diabetes m = 4·7 n = 256	5·0	11·7
Cardiovascular disease m = 5·1 n = 117	1·7	9·4
Renal disease m = 4·5 n = 120	2·5	7·5
Diseases of the sense organs m = 4·7 n = 75	5·3	6·7
Whole control series	7·7	15·3

m = average observation period for possession of a driving licence on special conditions (years).
n = number of drivers.

Percentage of drivers involved in crash and serious driving offenses within the investigation series divided into investigation and diagnostic groups, and in the control series

Key Question 1: Neurocognitive Evidence

Evans J, Wagner C, Welch J. Cognitive status in hemodialysis as a function of fluid adherence. Renal Failure 2004; 26: 575-581											
Key Questions Addressed	1		2		3		4				
	✓				✓						
Research Question	Comparison of cognitive function of hemodialysis patients to normative data, and influence of adherence to fluid intake on cognitive functioning for a group of hemodialysis (HD) patients										
Study Design	Historically controlled cohort										
Population	**Inclusion Criteria**	Individuals aged 18+ years receiving HD as a primary treatment for ESRD; ability to speak and understand English									
	Exclusion Criteria	Presence of a psychiatric disorder including clinical depression; living in an extended-care facility; receiving outpatient hemodialysis on a temporary basis following a peritoneal dialysis (PD) complication or transplant rejection; recently began HD therapy									
	Study population Characteristics	Variable	Adherent	Standardization Sample							
		n	47	NR							
		Age: (yrs.) mean ±SD	55.7±14.2	50.8							
		Gender M/F	38% M	Not reported							
		Duration on dialysis (yrs)	6.25±7.3	Not applicable							
		Ethnicity (% black)	66%	Not reported							
	Generalizability to CMV drivers	Unclear									
Methods	Patients were recruited from 3 dialysis clinics. Measurements of cognitive function were assessed by Cognistat, a 10 to 20 minute screening test to evaluate cognitive dysfunction in multiple, independent domains. Testing was undertaken during the first hour of dialysis.										
Statistical Methods	T tests, chi-square analyses, inferential analyses										
Quality assessment	Study quality	1	2	3	4	5	6	7	8	9	10
	Category: Low	No	S	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Relevant Outcomes Assessed	Cognitive function										
Results	Results for performance on Cognistat indicate rates of impairment ranging from 2.7% (orientation) to 54% (memory) for the entire sample size (Figure G-1). While slight impairment was demonstrated on tests for orientation, comprehension and naming, testing for memory, construction and similarities showed greatest impairment. A comparison of Cognistat scores of HD patients to standardization samples of the Cognistat demonstrated their performance to be most similar to a sample of healthy adults (average age of 50.8 yrs) and superior on all subscales versus a group of neurosurgical patients (average age of 54.2 yrs)(Table G-6). Scores for HD patients were similar to healthy adults with the exception of a lower score on the memory subscale (8.6±3.0 vs 11.5±0.7). With the exception of a significantly better performance by nonadherent pts on scores for calculation ($p<.05$), there was no significant differences on subscale performance in relation to fluid adherence. (Figure G-2).										
Authors' Comments	"Hemodialysis patients in this study exhibited cognitive impairment as measured by screening assessment." No direct relationship was found for fluid adherence and cognitive functioning.										

Figure G-1. Rate of Impairment on Cognistat Score (%)

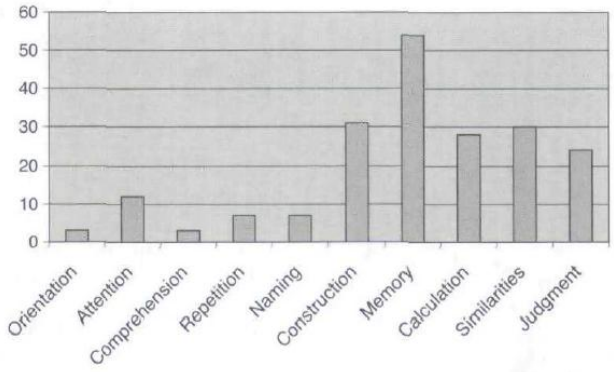
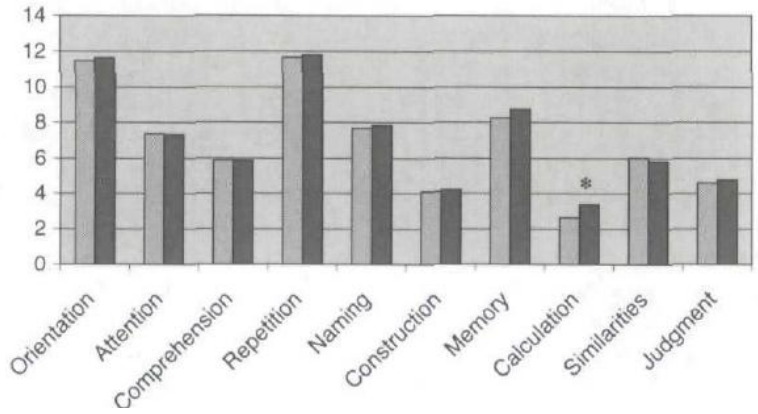


Table G-6. Comparison of Cognistat Scores

Cognistat subscale	Hemodialysis patients mean (SD)	Standardization sample mean (SD)	Neurosurgical sample mean (SD)
Orientation	11.6 (0.7)	12.0 (0.0)	10.5 (2.6)
Attention	7.3 (1.3)	7.1 (1.2)	6.3 (2.4)
Comprehension	5.9 (0.4)	6.0 (0.2)	5.0 (1.5)
Repetition	11.8 (0.9)	12.5 (0.8)	11.1 (2.9)
Naming	7.8 (0.6)	8.5 (0.7)	7.1 (2.1)
Construction	4.2 (2.0)	5.0 (0.4)	3.6 (1.8)
Memory*	8.6 (3.0)	11.5 (0.7)	6.3 (3.6)
Calculation	3.2 (1.4)	3.8 (0.6)	3.0 (1.5)
Similarities	5.9 (2.4)	6.1 (1.3)	4.3 (2.5)
Judgment	4.7 (1.4)	5.1 (0.5)	4.9 (1.3)

* p <0.1

Figure G-2. Cognistat Scores by Level of Fluid Adherence



† adherent; ■ non-adherent. * = *p* <.05

<table>
<tr><td colspan="11">Hart R, Pederson J, Czerwinski A, Adams R. Chronic Renal Failure, Dialysis, and Neuropsychological Function. Journal of Clinical Neuropsychology 1983; 5: 301-312</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="3">2</td><td colspan="3">3</td><td colspan="3">4</td></tr>
<tr><td>✓</td><td colspan="3"></td><td colspan="3">✓</td><td colspan="3"></td></tr>
<tr><td>Research Question</td><td colspan="10">Determine influence of dialysis on neuropsychological function</td></tr>
<tr><td>Study Design</td><td colspan="10">Cohort</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="9">62 patients aged 17-62 years; hemodialysis patients attending dialysis units at Oklahoma Memorial Hospital, the VA Hospital and Midwest Dialysis Center in Oklahoma City, OK; nondialyzed patients attended outpatient renal clinics at Oklahoma Memorial and VA Hospitals; controls attended outpatient clinics at O'Donahue Rehabilitation Center, an outpatient pain clinic at Oklahoma Memorial Hospital, an outpatient therapy group for individuals with physical disabilities at the VA Hospital, and the Paralyzed VA in Oklahoma. Two of the controls were inpatients (Neurology, Rehabilitation Medicine) at the VA Hospital.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="9">Individuals with sensory or motor disabilities which would adversely affect their performance on tasks</td></tr>
<tr><td>Study population Characteristics</td><td colspan="9">Variable | Hemodialysis Pts | Nondialyzed Renal Pts | Control
N | 24 | 18 | 20
Age (yrs) mean±SD | 40.3±13.1 | 43.0±11.9 | 40.5±11.3
Education (yrs) mean | 12.1±12.1 | 12.5±2.6 | 12.3±2.0
Gender M/F | 12/12 | 11/7 | 16/4
Ethnicity | 75% Caucasian | 67% Caucasian | 85% Caucasian

Duration Tx mean±SD 2.7±2.7 yrs
Length of time attending clinic (mean±SD): 5.1±5.5 yrs
Duration of chronic physical disabilities (mean±SD): 9.6±10.9 yrs</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="9">Unclear</td></tr>
<tr><td>Methods</td><td colspan="10">Diagnosis of dialysis and renal patients are listed in the table below. Patient assessments included psychometric measures of attention, recent memory and new learning, visuomotor speed and accuracy. See below for a test listing. Study participants were tested on various days; dialysis pts on a day they were not scheduled for dialysis, renal pts on a clinic visit or prior to hospital discharge, and controls were seen as outpatients.</td></tr>
<tr><td>Statistical Methods</td><td colspan="10">Multivariate analysis of variance, one-way analysis of variance, Duncan's Multiple Range Test, Pearson correlation coefficients</td></tr>
<tr><td rowspan="2">Quality Assessment</td><td rowspan="2">Internal Validity Category: Low</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr>
<tr><td>No</td><td>No</td><td>Yes</td><td>Yes</td><td>No</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="10">Neuropsychological function</td></tr>
<tr><td>Results</td><td colspan="10">Test performance scores are shown in An overall effect of Group, F (28, 92) = 2.1, P<.01 was found in a multivariate analysis of variance of the 14 measures of cognitive and perceptual-motor function. A one-way analysis of variance done for each individual measure indicated groups differed on 9/14 measures. Impaired performance by renal pts on all nine of these measures versus controls or to both controls and dialysis pts was measured in an individual comparison using Duncan's Multiple Range Test (p<0.5). Compared to controls, dialysis pts were only impaired on Visual Reproduction and performed worse than controls on 9/13 remaining measures. No significant correlations were found among dialysis pts for years of dialysis treatment and performance on any measure. In contrast, both blood urea nitrogen (BUN) and serum creatinine levels for renal clinic pts were highly correlated with performance on several tests. BUN and serum creatinine levels of renal pts were significantly correlated (r =.72, p<.0007).. In a comparison of "all renal pts" versus renal pts attending clinics for <6 months, data demonstrated that a shorter treatment time predicted less efficient performance (.Investigators concluded that the onset of treatment at a renal clinic seems to have beneficial effects on psychomotor efficiency and mental alertness.</td></tr>
<tr><td>Authors' Comments</td><td colspan="10">"The mild impairment n dialysis patients do not seem to be directly attributable to dialysis treatments. Rather, the onset of hemodialysis appears to have beneficial effects on neuropsychological function."</td></tr>
</table>

Table G-7. Diagnoses of Dialysis and Renal Clinic Patients

	Dialysis		Renal Clinic	
	$n = 24$		$n = 18$	
Diagnosis	n	+biopsy	n	+biopsy
Hereditary Nephritis	3	2	1	1
Polycystic Kidney Disease	3	–	3	–
Chronic Interstitial Nephritis	2	2	2	–
Chronic Interstitial Nephritis: Hypertension	4	2	2	–
Chronic Interstitial Nephritis: Obstruction	1	–	–	–
Chronic Interstitial Nephritis due to obstruction and infection	1	–	–	–
Glomerulonephritis	–	–	1	–
Glomerulonephritis - membrane proliferation	1	1	2	2
Glomerulonephritis, crescentic	1	1	1	1
Glomerulonephritis: Wegners Granuloma	1	1	–	–
Glomerulonephritis, Segroental Sclerosing	–	–	1	1
Lupus Nephritis	2	2	–	–
Glomerulosclerosis	1	1	–	–
Diabetic Glomerulosclerosis	4	2	5	1

Table G-8. Study Assessments

Test	Description
Mental Control	
Digit Span	
Logical Memory	
Visual Reproduction	
From the Wechsler Memory Scale	
Trial Making Tests (Parts A and B)	
WAIS Digit Symbol	
Digit Vigilance Test of the Rennick Repeatable Battery	
Purdue Pegboard (dominant hand)	
Free verbal learning task	Immediately recall 20 lists of common words. Each list was composed of 12 words presented auditory at a rate of 1 ½ s/word. All words were classified as A in the Thorndike-Lorge (1944) word count
Facial recognition memory task	48 faces were presented for 5 s each. 48 forced-choice recognition trials followed in which the original stimulus had to be chosen over a distracter.
Symbol digit paired-associate learning task	Subjects were to learn a list composed of eight relatively unfamiliar symbols, each paired with a one-digit number. For 3 s, subjects are shown each pair. Subjects are then shown the symbol and asked to retrieve the corresponding number. Each response was followed by correctly paired symbol-digit for 3 s. Four test trials were performed.

Table G-9. Test Performance

Measure	Dialysis $n=24$ M	Dialysis $n=24$ SD	Renal Clinic $n=18$ M	Renal Clinic $n=18$ SD	Controls $n=20$ M	Controls $n=20$ SD	F	p
Age	40.3	13.1	43.0	11.9	40.5	11.3	<1	NS
Education	12.1	2.7	12.5	2.6	12.3	2.0	<1	NS
Beck Depression	12.0	6.2	9.2	6.3	14.1	8.5	2.33	NS
Mental Control	6.5	1.9	6.0	2.1	6.5	1.9	<1	NS
Digit Span Forward	5.8	1.0	6.0	1.3	5.9	1.4	<1	NS
Digit Span Backward	4.7	1.1	4.1	0.8	4.6	1.2	1.92	NS
Digit Vigilance-Time	203.3	38.2	270.2**	99.9	201.0	43.6	7.27	.002
Digit Vigilance-Error	3.6	3.3	8.2**	11.1	2.8	3.4	3.76	.03
Trails A	31.2	10.1	46.8**	21.5	35.3	13.1	5.69	.006
Trails B	92.8	47.4	146.7**	74.5	81.9	22.9	8.59	.001
Digit Symbol	47.0	8.9	40.8*	12.2	48.7	10.5	3.01	.06
Logical Memory	8.7	2.9	7.0*	2.7	10.2	2.9	6.02	.005
Visual Reproduction	8.3*	3.0	6.8*	3.2	10.2	2.4	6.62	.003
Word List	89.0	20.2	87.7	16.4	87.3	8.6	<1	NS
Facial Memory	37.3	5.2	33.5**	6.0	38.8	5.0	4.74	.02
Symbol-Digit Paired Associates	21.8	8.3	19.4	7.5	23.0	6.6	1.06	NS
Purdue Pegboard (D)	11.8	2.5	11.4*	2.2	13.1	1.6	3.15	.05

* $p<0.05$ compared to controls, Duncan's Multiple Range Test

** $p<.05$ compared to both dialysis patients and controls, Duncan's Multiple Range Test

Table G-10. Correlations Between BUN and Creatinine With Test Performance in Renal Clinic Patients

Measure	r with BUN	p	r with Cr	p
Digit Vigilance Time	.68	.002	.51	.03
Digit Symbol	−.56	.02	−.41	.06
Purdue Pegboard (D)	−.53	.02	−.40	.06
Digit Span Forward	−.45	.05	−.18	.25
Facial Memory	−.23	.20	−.35	.09

Table G-11. Intercorrelation (r) Among Test Scores in Renal Clinic Patients

Intercorrelation (r) Among Test Scores in Renal Clinic Patients

	Digit Vigilance Time	Trail A	Trail B	Digit Symbol	Purdue Pegboard
Digit Vigilance Time	-----				
Trail A	.73 $p<.001$	-----			
Trail B	<.57 $p<.02$	.74 $p<.0005$	-----		
Digit Symbol	−.67 $p<.003$	−.79 $p<.0001$	−.83 $p<.0001$	-----	
Purdue Pegboard	−.60 $p<.009$	−.70 $p<.002$	−.82 $p<.0001$	.86 $p<.0001$	-----

Table G-12. Mean Performance Ratings and Age-corrected Scaled Scores

Measure	Controls $n=20$	Dialysis Patients $n=24$	All Renal Clinic Patients $n=18$	Renal Clinic Patients Attending Clinic > 6 mo. $n=13$
Logical Memory[a]	1.9	2.7	3.5	3.2
Visual Reproduction[a]	1.3	2.0	2.7	2.4
Trail Making Test, Part A[b]	1.6	1.4	2.3	1.8
Trail Making Test, Part B[b]	1.2	1.4	2.6	1.9
Digit Vigilance[c]	1.7	1.8	2.4	2.2
Digit Symbol[d]	9.2	8.7	7.9	8.2

Note: Higher rating (all tests except Digit Symbol) indicates greater performance impairment.

a 0-5 rating from Russell (1975)

b 0-5 rating from Russell, Neuringer, and Goldstein (1970)

c 0-4 rating from Rennick Repeatable Battery

d Age-corrected scaled scores

<table>
<tr><td colspan="4">Kramer, L., Madl, C., Stockenhuber, F., Yeganehfar, W., Eisenhuber, E., Derfler, K., Lenz, K., Schneider, B., Grimm, G. Beneficial Effect of Kidney transplantation on Cognitive Brain Function. Kidney International; 49: 833-838. (1996).</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td></tr>
<tr><td>✓</td><td></td><td></td><td>✓</td></tr>
<tr><td>Research Question</td><td colspan="4">Does kidney transplantation improve cognitive functioning among persons with ESRD enrolled in hemodialysis?</td></tr>
<tr><td>Study Design</td><td colspan="4">Cohort controlled; Pre-Post Measures of Cases</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="3">Cases: Outpatients associated with the Departments of Medicine III and IV, University of Vienna, Austria enrolled in hemodialysis treatment due to ESRD and candidates for either cadaveric or living-donor kidney transplantation.
Controls: Volunteers associated with the University of Vienna with no evidenced kidney disease.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="3">Persons who were psychiatrically impaired, as scored by screening exam, those evidenced having neurological, vascular or immunological complications. Persons with systemic diseases such diabetes, malignant hypertension and multiple myeloma were also excluded.</td></tr>
<tr><td>Study population Characteristics</td><td colspan="3">
<table>
<tr><td>Measure</td><td>Case</td><td>Control</td></tr>
<tr><td>Population (n)</td><td>15</td><td>45</td></tr>
<tr><td>Age y</td><td></td><td></td></tr>
<tr><td>(mean ± SD)</td><td>45 ± 13</td><td>NR</td></tr>
<tr><td>Male %</td><td>7 (47%)</td><td>NR</td></tr>
<tr><td>Duration of Dialysis</td><td></td><td></td></tr>
<tr><td>Median mos.</td><td>16</td><td>NA</td></tr>
<tr><td>Range mos.</td><td>3 – 96</td><td>NA</td></tr>
<tr><td>Comorbid Condition:</td><td>8/15 (53%)</td><td>NA</td></tr>
</table>
</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="3">Unclear</td></tr>
<tr><td>Methods</td><td colspan="4">With the approval of the Internal Review Board, informed consent was given by participants for study inclusion.
Out of a total pool of 169 available volunteers, 45 were chosen for gender and age-match to ESRD/Trans participants (data not shown). Controls submitted to blood sampling.
ESDR/Trans participants were tested no more than 24 hours after a routine hemodialysis session, establishing baseline measures for cognitive functioning as described below and recent serum analyses.
Measures of Cognitive Functioning:
Evoked Potential Measures (EPM): electrical impulses as recorded through electrodes places on face and skull. Pip tones were binaurally channeled through earphone connection.EEG epogues were of 800 ms were electronically recorded after each tone and electronically recorded. Troughs and peaks were calculated to P300 (latency) and N400 (amplitude) and according to standard methods for the electrodiagnostic system.
Trailmaking Test: Tucson: Neuropsychology Test, 1982. Short-term memory and sensorimotor reaction time.
Mini-mental State: screening for neuropathology, severe psychiatric illness for clinicians, 1975.
Serum Measures:
Hemoglobin g/dl
Hematocrit %
Creatinine mg/dl
BUN mg/dl
To evaluate the effect of hemoglobin levels on cognitive functions, 6 patients from the same case census (in hemodialysis) were chosen for data comparison. These patients had normal hemoglobin levels. Six patients (in hemodialysis) with severe anemia were also selected. Patient participants were given same battery of tests.
ESDR/Trans participants were again given the battery of tests and serum measures about a year after kidney transplantation (14 ± 5 mos.).
Researchers note that will transplantation-related chemotherapy to reduce complications and graft rejection commenced at time of surgery. The regimen included cyclophosphamide (n=10), prednisolone (n=10) and five (5) patients received azathioprine. All received recombinant erythropoietin therapy. One patient received therapy to control for HLA-antibodies.</td></tr>
</table>

Statistical Methods	Results obtained at baseline and after transplantation were compared using Student's t-test or Wilcoxin test for paired data. Tests of data normality were performed using the Wilk-Shapiro method. Comparison of within and between groups was performed with either ANOVA or the Wilcoxon test for paired data. Associations of all research variables were investigated using the Pearson or Spearman correlations coefficients.										
Quality assessment	**Study quality** Category**:**	1	2	3	4	5	6	7	8	9	10
	Moderate	No	S	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Relevant Outcomes Assessed	Pre- and post-transplantation serum and cognitive function measures within and between case and control group comparison.										
Results	Before transplantation, researchers demonstrated a significant correlation among and between these measures: P300 latency (EPM) which detected poor cognitive functioning among ESDR/Trans group in with age, hemoglobin, hematocrit, BUN levels compared to matched group ($p < 0.01$). No significant correlation between electrophysiological data and blood assay measures was detected. Post-transplantation, age was the only parameter correlated to P300 (poor cognitive function) among the case group. This same correlation was found in the control subjects ($p < 0.05$) Following kidney transplantation (approx. 14 mos. Post-graft) EPM (2 central indices of cognitive functioning) scores described above significantly improved compared to baseline scores ($p < 0.01$; $p < p\ 0.05$). Post-transplantation patients (14 mos.) showed no significant differences in EPM, Trailmaking Tests and Mini-Mental State Tests compared with matched control group.										
Authors' Comments	Researchers conclude that cognitive dysfunction among HD patients , with successful kidney transplantation may be fully reversed. These reversals and improvements in cognitive functioning, with transplantation, are evident in those patients who have been in HD treatment for long periods of time..										

Murray A, Tupper D, Knopman D, Gilbertson D, Pederson S, Li S, Smith G, Hochhalter A, Collins A, Kane R. Cognitive Impairment in Hemodialysis Patients Is Common. Neurology 2006; 67; 216-223

Key Questions Addressed	1	2	3	4
	✓		✓	

Research Question: Cognitive performance of hemodialysis patients

Study Design: Cohort controlled

Population

Inclusion Criteria: Individuals aged 55+ years on maintenance hemodialysis for at least 2 months at one of 16 clinics in Minneapolis and St. Paul, MN; English as their primary language

Exclusion Criteria: Controls were excluded if diagnosed with ESRD or chronic kidney disease (CKD). Individuals were excluded from entire study if previously diagnosed with dementia or International Classification of Disease, Ninth Edition, Clinical Modification equivalents to avoid high population severe cognitive impairments

Study population Characteristics

Variable	Hemodialysis patients		
	Primary Cohort	Random Sample	Non-dialysis comparison
n	338	101	101
Age			
55-64	29.5	30.7	40.6
65-74	31.7	34.7	34.7
75-84	30.8	27.7	17.8
≥85	8.0	6.9	6.9
Mean	71.2±9.5	70.4±9.4	68.5±9.6
Gender (female)	45.9	43.6	55.4
Dialysis, mo			
0-12	28.1	32.7	
13-24	24.0	20.8	
>24	47.9	46.5	
Mean duration	32.8±32.8	35.5±42.2	

Generalizability to CMV drivers: Unclear

Methods: Dialysis patients were tested once during a 2-day dialysis cycle; 1 hour before dialysis, 1 hour after, or on an "off day". A non-dialysis comparison group of 101 individuals was recruited from outpatient clinics and from the general community. A random sample of 101 hemodialysis patients matched by age was obtained from the 338 individuals in the primary cohort. Participants were administered nine neuropsychological tests over 45 minutes. Testing included Hopkins Verbal Learning Test-Revised (HVLT-R), Color Trails 1 and 2, Stroop Interference Test, Brief Visuospatial Memory Test-Revised (BVMT-R), Controlled Oral Word Association (COWAT), Clock-drawing Test, and Wechsler Digit Span. Using the algorithm shown in

Table G-13 cognitive impairment of individuals was divided into the following categories: no, mild, moderate, or severe.

Statistical Methods: Bivariate analysis; logistic regression

Quality assessment

Study Quality Assessment: Moderate	1	2	3	4	5	6	7	8	9	10
	No	S	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Results: Percentage of the 338 primary cohort who scored ≤1.49 SD, 1.50 – 1.99 SD, and ≥ SD below the age-adjusted norm for cognitive testing is shown in Table G-14. Only 11% scored ≥2.00 SD below the norm on verbal function test (COWAT) however between 35% – 40% scored ≥2.00 SD below the norm on tests for memory and executive function domains (Color Trails 2 , 35.8%; BVMT-R, 35.6%; Stroop Interference Test, 41.1%). Frequency of cognitive impairment in the primary hemodialysis patient sample is shown in Table G-

	15. Results show >70% of the 338 sample group had moderate or severe cognitive impairment (37% severe, 36% moderate); while <30% had mild or normal cognition. Further analysis determined an association among others of duration of dialysis (>24 months) and vascular primary causes of ESRD with severe cognitive impairment (Table G-16). In a comparison of the 101 randomly selected hemodialysis subjects and the nondialysis control group significantly higher cognitive impairment (33.7% vs 11.9%) (Figure G-3) was demonstrated by the HD group. Grouped by age results included severely impaired aged 55-64, 29.0% vs 12.2%; severely impaired aged 65-74, 34.3% vs 5.7%; severely impaired aged 75-84, 32.1% vs 11.1%. In a logistic regression model combining the two groups (n=202), the HD subjects had a high risk of severe cognitive impairment relative to the control group (adjusted OR 3.54; 95% CI, 1.28, 9.78; p <0.02), adjusted for age, gender, ethnicity, education, depression, diabetes, hypertension, and stroke.
Authors' Comments	A high rate of moderate to severe undiagnosed cognitive impairment was found in this HD study population. Investigators recommend initiatives to assess cognitive function for patients prior to beginning dialysis and afterward.

Table G-13: Cognitive Impairment Algorithm

1. Normal: scored ≤1.49 SD below the age-adjusted mean on all tests in all domains*
2. Mild cognitive impairment: scored 1.50 to 1.99 SD below the age-adjusted mean in ≤1 domain
3. Moderate cognitive impairment: scored 1.50 to 1.99 SD below the age-adjusted mean on one or more tests in >1 domain, or ≥2.00 SD below the mean in ≤1 domain
4. Severe cognitive impairment†: scored ≥2.00 SD below the age-adjusted mean on at least one test in ≥2 domains

* The cognitive domains of memory, executive function, and language.
†Classification as severe cognitive impairment requires results of at least one test in each of two or more of the three domains.

Table G-14. Mean Scores (SD) Below Adjusted Means in Primary Hemodialysis Cohort (n=338)

Cognitive test	Raw score, mean (SD)	Percent by number of SDs below adjusted population norms*		
		<1.50	1.50–1.99	≥2.0
3MS (total score)	88.3 (8.6)	59.5	27.5	13.0
Hopkins Verbal Learning (delayed, words)	5.1 (3.2)	48.5	13.3	38.2
Color Trails 2 (time, s)	156.5 (53.9)	57.0	7.2	35.8
BVMT-R (delayed, figures)	4.7 (3.0)	45.8	18.6	35.6
Stroop Interference Test (s)	110.4 (43.3)	49.9	9.0	41.1
COWAT (total words)	26.4 (11.1)	71.3	17.8	10.9
Digit Span	14.7 (3.8)	96.1	3.9†	
Clock-drawing	3.3 (0.8)		26.2‡	
Geriatric Depression Scale	3.2 (2.7)		24.9§	

3MS= Modified Mini-Mental State Examination; BVMT-R= Brief Visuospatial Memory Test Revised;
COWAT= Controlled Oral Word Association Test (given to a subset of 101 of the primary hemodialysis patient cohort).
* Published normative scores were adjusted for age for the Hopkins, BVMT-R, and Stroop; for age and education for Color Trails; and for age, education, and ethnicity for the COWAT.
† 3.9% scored >1.50 SD below normal mean
‡ 26.2% scored ≤ 2 out of 4

Table G-15. Frequency of Cognitive Impairment in Primary Hemodialysis Cohort (n=338)

Characteristic	n	Percent with cognitive impairment: None, n = 43	Mild, n = 47	Moderate, n = 122	Severe, n = 126
Age, y					
55–64	100	12.0	10.0	37.0	41.0
65–74	107	14.0	11.2	36.5	38.3
75–84	104	12.5	21.2	34.6	31.7
≥85	27	11.1	11.1	37.0	40.8
Sex					
Female	155	12.3	9.7	40.7	37.4
Male	183	13.1	17.5	32.2	37.2
Education, y					
0–8	38	5.3	7.9	31.5	55.3
9–12	147	9.5	10.2	39.5	40.8
>12	153	17.6	19.0	34.0	29.4
Race					
White	279	15.1	15.8	35.5	33.7
Black	38	0.0	5.3	42.1	52.6
Other	21	4.8	4.8	33.3	57.1
Total	338	12.7	13.9	36.4	37.0

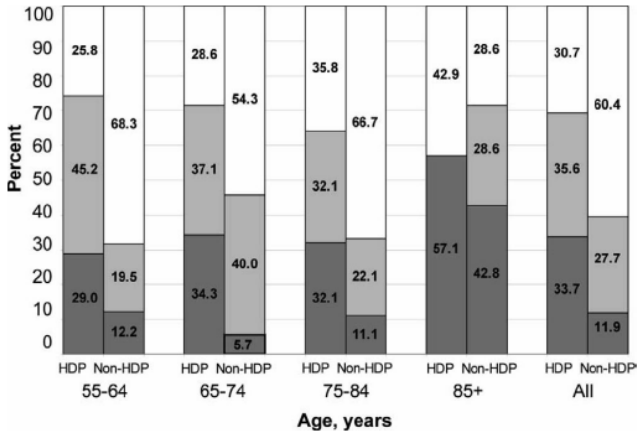
Table G-16. Characteristics Associated With Severe Cognitive Impairment in Primary Hemodialysis Patient Cohort (n=338)

Characteristic	n	Percent with severe cognitive impairment: Yes	No	p*	Adjusted OR (95% CI)	p†
Age, y				0.540		
55–64	100	41.0	59.0		reference	
65–74	107	37.4	62.6		0.77 (0.42, 1.43)	0.410
75–84	104	31.7	68.3		0.57 (0.29, 1.10)	0.090
≥85	27	40.8	59.2		1.05 (0.40, 2.77)	0.910
Sex				0.960		
Female	155	36.7	63.3		0.82 (0.50, 1.35)	0.440
Male	183	37.2	62.8		reference	
Race				0.010		
White	279	33.3	66.7		0.53 (0.24, 1.15)	0.110
Black	38	52.6	47.4		reference	
Other	21	57.1	42.9		1.26 (0.39, 4.10)	0.710
Education, y				0.010		
0–8	38	55.3	44.7		reference	
9–12	147	40.1	59.9		0.42 (0.19, 0.92)	0.030
>12	153	29.4	70.6		0.32 (0.14, 0.72)	0.006
Stroke	70	45.7	54.3	0.100	1.95 (1.08, 3.49)	0.030
Hemoglobin, g/dL‡				0.030		
0.0–10.9	54	50.0	50.0		reference	
≥11.0	282	34.4	65.6		0.56 (0.29, 1.08)	0.080
Months of dialysis				0.050		
0–12	95	28.4	71.6		reference	
13–24	81	33.3	66.7		0.95 (0.47, 1.91)	0.870
>24	162	43.8	56.2		1.65 (0.91, 3.00)	0.100
Primary cause of ESRD						
Vascular				0.030	0.64 (0.33, 1.25)	0.190
Diabetes	131	42.0	58.0			
Hypertension	111	35.1	64.9			
Glomerulonephritis	32	43.8	56.2			
Nonvascular					reference	
PKD	20	20.0	80.0			
Interstitial nephritis	15	20.0	80.0			
Neoplasms, tumors	3	33.3	66.7			
Miscellaneous	26	34.6	65.4			
Equilibrated Kt/V (dialysis dose)‡						
0.0–1.2	148	31.8	68.2	0.070	reference	
>1.2	181	40.9	59.1		1.67 (1.01, 2.75)	0.050

The X^2 test was used for comparisons between categorical variables. Analysis of variance was used for between-group comparisons.
* P For bivariate comparisons between those with and without severe cognitive impairment.
† On logistic regression
‡ Hemoglobin data were missing for two subjects; Kt/V data were missing for nine subjects.

ESRD= end-stage renal disease; PKD=polycystic kidney disease

Figure G-3. Frequency of Cognitive Impairment



Frequency of cognitive impairment in hemodialysis patient (HD) random sample (n=101) and age-matched non-hemodialysis patient sample (n=101). White = normal to mild, light gray = moderate, dark gray = severe cognitive impairment

Pereira A, Weiner D, Scott T, Chandra P, Bluestein R, Griffith J, Sarnak M. Subcortical Cognitive Impairment in Dialysis Patients. Hemodialysis International 2007; 11: 309-314											
Key Questions Addressed	1		2		3		4				
	✓				✓						
Research Question	Level of cognitive impairment of dialysis patients										
Study Design	Historically-controlled cohort										
Population	**Inclusion Criteria**	Patients enrolled from the Dialysis Clinic Inc., Boston hemodialysis unit; aged ≥18 yrs, fluent in English, with MMSE score ≥24; must have been on dialysis for at least 1 month and have Kt/V ≥ 1.2 and hematocrit > 30%.									
	Exclusion Criteria	Individuals with a history of prior stroke, were hospitalized within one month, unable to participate in the neuropsychological survey, or unable to read large font (14 pt. Times New Roman).									
	Study population Characteristics	Variable	Value								
		n	25								
		Age (yrs)	68.6±12.7								
		Gender M/F	11/14								
	Generalizability to CMV drivers	Unclear									
Methods	Subject testing included Block Design, Digit Symbol-Coding and Trail Making Tests (A and B).										
Statistical Methods	Chi-square test, *t* test										
Quality Assessment	**Internal Validity**	1	2	3	4	5	6	7	8	9	10
	Category: Low	No	S	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Relevant Outcomes Assessed	Cognitive impairment										
Results	Cognitive test results are shown in Table G-17. While tests of premorbid intelligence, retention and recognition were similar in comparison to population norms, significant deficits were seen in tests of subcortical or executive function; WAIS-III symbol coding (7.7±3.1 vs 10±3, p=0.001), WAIS-III block design (7.0±1.7 vs 10±3, p<0.001), Trail A (40.5±8.3 vs 50±10, p<0.001) and Trail B (41.8±11.3 vs 50±10, p<0.001).										
Authors' Comments	Mild cognitive impairment was found in this small population of hemodialysis patients.										

Table G-17. Cognitive Test Results

	Function assessed	Consented sample		Normative data	
		Mean ± SD	Median	Reference ± SD	p value
MMSE	Cognitive screening	27.5 ± 2.3	28	"Normal" ≥24	NA
NAART verbal intelligence quotient	Intelligence	99.5 ± 11.9	100	100 ± 15	0.83
WMS-III Retention	Primarily cortical	11.2 ± 2.6[a]	10	10 ± 3	0.03
WMS-III Recognition		9.1 ± 3.5[a]	9	10 ± 3	0.31
WAIS-III Block design	Primarily subcortical	7.0 ± 1.7[a]	8	10 ± 3	<0.001
WAIS-III Symbol coding		7.7 ± 3.1[a]	7	10 ± 3	0.001
Trail A		40.5 ± 8.3[b,c]	41	50 ± 10[c]	<0.001
Trail B		41.8 ± 11.3[b,c]	43	50 ± 10[c]	<0.001
CESD	Depression	7.8 ± 6.5	6	Depression likely present when CESD>16	Two subjects (16%) had scores>16

[a] Normalized for subject age
[b] Normalized for age, gender, and education level
[c] T scores for test performance
CESD = Center for Epidemiological Studies of Depression Scale; age and education associated norms; MMSE= Mini-Mental State Exam; NA = Not applicable; NAART=estimated verbal intelligence quotient from the North American Adult Reading Test; WAIS=Wechsler Adult Intelligence Scale; WMS=Wechsler Memory Scale

Pliskin N, Yurk H, Ho L, Umans J. Neurocognitive Function in Chronic Hemodialysis Patients. Kidney International 1996; 49: 1435-1440										
Key Questions Addressed	1	2	3	4						
	✓									
Research Question	Level of neuropsychological dysfunction in chronic hemodialysis patients									
Study Design	Cohort									
Population	**Inclusion Criteria**	Individuals with ESRD (primarily due to hypertension – 50% of sample) and diabetes (26%) on chronic hemodialysis; of African-American descent; have been receiving high-flux hemodialysis 3x/wk for at least 6 months. Controls all had chronic medical conditions including osteoarthritis (4), diabetes and hypertension (4), and rheumatoid arthritis (4).								
	Exclusion Criteria	Individuals missing >1 dialysis tx/mo, predialysis serum phosphorous ≥7.0, or interdialytic weight gain >3.5 kg; history of unstable coronary disease evidenced by unstable angina or known MI, cerebrovascular disease noticeable by new, transient or fixed neurologic deficits, or uncontrolled hypertension during the past 6 months, or collagen vascular disease or vasculitis requiring administration of any cytotoxic agents or glucocorticoids (at doses exceeding 10 mg prednisone/day); with refractory anemia (hgb less than 9 g/dl) despite erythropoietin therapy and supplemental iron, and patients with evidence of protein malnutrition [serum albumin < 3.5 g/dl or protein catabolic rates (PCR) < 0.8]								
	Study population Characteristics	Variable	Case	Control						
		n	16	12						
		Age: (yrs.) mean ±SD	59.8±15.5	58.7±12.3						
		Education	10.4±3.6	11.2±1.1						
		Gender M/F	7/9	2/10						
		Measured Kt/V	1.46±0.24 (range 1.16 to 2.03)							
		PCR	1.07±0.23 (range 0.8 to 1.5)							
	Generalizability to CMV drivers	Unclear								
Methods	Control patients were recruited from medical and rheumatology clinics and matched to study population by age, education and ethnicity. Their chronic medical condition required clinic follow-up of 3x/yr. None had serum creatinine ≥2.0 mg/dl. Case and control groups were administered a battery of neuropsychological tests to assess intelligence (Wechsler Adult Intelligence Scale-Revised; WAIS-R); immediate and delayed memory (Wechsler Memory Scale (WMS); attention/mental processing speed (PASAT, Trail Making Test; Stroop Color-Word Test); language abilities (Boston Naming Test, Controlled Oral Word Association); complex problem solving (Tactual Performance Test, Category Test); and motor abilities (Finger Tapping Test).									
Statistical Methods	ANOVA									
Quality assessment	Study quality	1	2	3	4	5	6	7	8	9	10
	Quality category: Moderate	No	S	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Relevant Outcomes Assessed	Neurocognitive function										
Results	Scores for memory, language and complex problem solving did not differ between groups (Table G-18). While deficit scores for ESRD patients were found for some attention/mental processing scores (Stroop Word, p ≤0.03 and Color Reading, p ≤0.04), results on similar tests for attention (Trailmaking A (37.3±8.7 vs 36.1±7.6), PASAT(i.e., Trial 2 (-1.8±.78 vs -1.4±1.0), and Stroop Color Word (35.6±7.2 vs 35.2±8.8) did not differ between groups.									
Authors' Comments	Mild neurocognitive impairment was found in this small population of chronic hemodialysis patients.									

Table G-18. Neuropsychological Testing

	ESRD (N = 16) mean (SD)	Controls (N = 12) mean (SD)	P
Age	59.8 (15.5)	58.7 (12.3)	NS
Education	10.4 (3.6)	11.2 (1.1)	NS
Beck Depression Score	12.2 (8.6)	6.0 (4.4)	NS
Intelligence			
Verbal IQ	86.2 (8.9)	85.8 (9.5)	NS
Performance IQ	84.5 (11.6)	82.3 (9.2)	NS
Full Scale IQ	84.7 (9.5)	84.0 (9.0)	NS
Information	8.4 (2.1)	7.1 (1.6)	NS
Digit Span	7.7 (2.0)	8.3 (2.2)	NS
Vocabulary	8.1 (1.8)	7.4 (2.0)	NS
Arithmetic	7.1 (1.9)	8.0 (1.9)	NS
Similarities	8.1 (2.0)	7.8 (2.6)	NS
Picture Compl.	7.9 (3.4)	6.8 (2.0)	NS
Picture Arr.	8.8 (2.5)	7.3 (1.6)	NS
Block Design	7.5 (2.3)	6.6 (3.0)	NS
Obj. Assembly	6.6 (2.0)	7.6 (1.9)	NS
Digit Symbol	6.6 (2.0)	7.6 (1.9)	NS
Memory			
Wechsler Memory Scale:			
Memory Quotient	100.3 (15.2)	98.8 (13.0)	NS
Immediate Verbal	17.7 (5.7)	17.8 (6.6)	NS
Delayed Verbal	14.7 (5.5)	15.6 (5.9)	NS
Verbal % Retained	87.0 (15.9)	89.8 (13.1)	NS
Immediate Visual	6.9 (3.3)	6.5 (3.3)	NS
Delayed Visual	5.7 (3.1)	5.3 (2.4)	NS
Visual % Retained	80.6 (27.2)	88.4 (37.4)	NS
Attention/mental processing speed			
PASAT (Z-Score)			
Trial 1	−2.1 (.83)	−1.5 (.97)	NS
Trial 2	−1.8 (.78)	−1.4 (1.0)	NS
Trial 3	−1.4 (.60)	−1.1 (.56)	NS
Trial 4	−1.0 (.63)	−0.9 (.57)	NS
Stroop (T-Score)			
Word	32.2 (7.3)	38.2 (5.7)	0.03
Color	31.3 (10.8)	39.2 (6.4)	0.04
Color-Word	35.6 (7.2)	35.2 (8.8)	NS
Trailmaking (T-Score)			
Part A	37.3 (8.7)	36.1 (7.6)	NS
Part B	35.5 (6.5)	35.0 (10.9)	NS
Language			
Boston Naming Test (Z-Scores):	−3.2 (2.7)	−4.4 (5.9)	NS
Word Fluency:	36.8 (7.6)	33.8 (10.7)	NS
Aphasia Screen Test:	43.4 (12.2)	46.3 (14.1)	NS
Complex problem solving			
Tactual Performance Test (T-Scores):			
Dominant	37.3 (11.2)	42.2 (8.5)	NS
Nondominant	36.6 (8.0)	40.2 (3.8)	NS
Both Hands	40.2 (6.7)	40.6 (5.8)	NS
Total Time	38.5 (9.0)	41.4 (6.0)	NS
Memory	39.2 (7.0)	35.8 (8.0)	NS
Location	44.7 (6.5)	41.0 (6.4)	NS
Category Test: (T-Scores)	35.6 (7.9)	35.0 (9.1)	NS
Motor skills Finger Tapping (T-Scores):			
Dominant	37.3 (8.8)	38.6 (8.1)	NS
Nondominant	35.9 (9.7)	36.1 (9.3)	NS
Grip Strenth (T-Scores):			
Dominant	35.7 (7.5)	52.3 (6.6)	0.0001
Nondominant	38.1 (8.8)	55.1 (6.8)	0.001

Demographic Information and Neuropsychological Test Performance in ESRD Patients and Controls

<table>
<tr><td colspan="11">Thornton, W.L., Shapiro, R.J., Deria, S., Gelb, S., Hill, A., Differential Impact of Age on Verbal Memory and Executive Functioning in Chronic Kidney Disease. Journal of International Neuropsychological Society, 2007, 13: 344-353</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="3">2</td><td colspan="3">3</td><td colspan="3">4</td></tr>
<tr><td>✓</td><td colspan="3"></td><td colspan="3"></td><td colspan="3"></td></tr>
<tr><td>Research Question</td><td colspan="10">How do persons with chronic kidney disease (CKD) compare with otherwise healthy adults of the same age in cognitive functioning when controlling for age, severity of illness and psychological depression?</td></tr>
<tr><td>Study Design</td><td colspan="10">Cohort; Multi-measures; Age - Equivalent Group Comparisons</td></tr>
<tr><td rowspan="3">Population</td><td>Inclusion Criteria</td><td colspan="9">Cases: Outpatient sample of 51 consecutive CKD persons referred to Vancouver General Hospital for treatment. Subjects' serum analysis yield GFR in the range < 60mL/min/1.73 m^2; <u>not</u> receiving hemodialysis or peritoneal dialysis; had attained at least 6 yrs of primary education; were followed by renal clinic for at least 6 mos. prior to study intake; natural or corrected visual acuity could not fall below 20/50.
Controls: Healthy respondents with no diagnosed kidney disease, assessed by self-report, matched on age, gender, educational attainment and visual acuity; drawn from the same community cohort as CKD patients.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="9">No overt CNS or related pathologies such as major psychiatric illness, organ failure, stroke, dementia, head injury, CNS malignancy, Parkinson's Disease or similar in current or prior medical history.</td></tr>
<tr><td>Study population Characteristics</td><td colspan="9"><table><tr><td><u>Measure</u></td><td><u>Case</u></td><td><u>Control</u></td></tr><tr><td>Population (n)</td><td>51</td><td>55</td></tr><tr><td>Age y (Mean ± SD)</td><td>63.24 ± 13.57</td><td>60.53 ± 15.15</td></tr><tr><td>Female %</td><td>27 (53%)</td><td>34 (62%)</td></tr><tr><td>Education y (Mean± SD)</td><td>13.41 ± 3.16</td><td>14.13 ± 2.29</td></tr></table></td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="9">Unclear</td></tr>
<tr><td>Methods</td><td colspan="10">Tests were individually administered to subjects by trained researchers according to standard procedures.
Participants received remuneration for time and travel.
Measures include:
Vocabulary: untimed multiple choice adapted from ETS kit (Ekstrom et al) for measure of general intelligence.
Verbal Learning & Memory: asses learning over repeated trials; delayed recall provides estimate of retention.
Executive Function: "Mental Shifting" or ability to transfer learning tasks to a similar learning task and cognitive "inhibition" are the two variables measured, i.e., facility and speed of problem-solving.
Depression: Standard test (CES-D) assessing depressive thoughts, behaviors.
Instrument of Activities of Daily Living: assess ability to living independently; level of autonomy.
Health Questionnaire: Assess current health status and medical history.
Lab Measures:
Serum assays for metabolic compensation, GFR, hemoglobin (Case Group only).</td></tr>
<tr><td>Statistical Methods</td><td colspan="10">Sample difference across the demographic, depression and cognitive performance measures were examined with independent t-tests or nonparametric tests (Pearson Chi-square) where appropriate.
Age categories were presented as "All" "Younger (30 to 60 y)" and "Older (61 to 89 y)".
A composite T-score based on the control mean was used to reduce the number of dependent variables for subsequent projective tests.
Independent and matched scores analyses.
Two variables for Executive Function, set shifting and inhibition, found to be significantly independent, were entered separately into subsequent predictive models.
For case and controls, distributions were analyzed for skewness and extreme values and were adjusted for rank-order sequence. Four subjects in all were found to be outliers for Executive Function factors.
To place the scores on a consistent metric, T-scores were calculated (Mean: 50 ± 10).
Pearson correlation of all continuous independent measures: age, education, GFR, Hemoglobin and cognitive performance factors.
Two-step hierarchical model to examine predictive value of age and health status on cognitive functioning.
A two-tailed $p < 0.05$ was selected for significance testing.
Analyses were performed using SPSS V14.0 software.</td></tr>
<tr><td>Quality assessment</td><td>Study quality</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr>
</table>

	Quality Category: Moderate	No	S	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Relevant Outcomes Assessed	Equivalence between Case and Controls on demographic and medical history categories. Presence of cognitive impairment an, and the severity of impairment as indexed by GFR and hemoglobin scores. Interaction of age, depression, and presence of CKD and their predictive values on impairment dimensions Pearson *r* scores of all independent continuous variables.										
Results	Overall, adults with CKD demonstrate higher rates of cognitive impairment relative to matched controls. These impairments become more pronounced for the CKD persons aged 61 years and older. No differences between case and controls for ability for independent living, age, education, vocabulary or gender ratio. CKD group had a significantly higher proportion of persons with diabetes and hypertension than control group, as expected. CKD group, on average, had been diagnosed with kidney disease for 5.6 y ± 6.7 y. Over half (55%) had Stage 4 CKD with an average GFR of 24.11 ± 11.05 mL/min/1.73 m^2 (moderate to severe). There was no direct association between increasing age and severity of kidney disease. Rather, age was evenly distributed across all stages (severity) of chronic kidney disease. Age, however, was significantly correlated with poorer cognitive performance within the CKD group. CKD patients reported higher number of depression symptoms than controls. However, when stratified by age, younger CKD participants (those <=60 y) were significantly more likely than older CKD to report depression symptoms. Depressive symptoms, however, were not a significant predictor of either verbal memory or mental shifting, affirming the findings above that with increase aging there was a linear relationship to fewer depressive symptoms and better performance on cognitive inhibition. GFR scores (severity classification of disease status) and hemoglobin scores were not correlated to cognitive performance. The CKD (younger and older) scores were significantly poorer than controls on delayed verbal learning and memory recall performance. Older CKD participants scored significantly poorer scores on mental shifting and cognitive inhibition. Younger CKD participants' scores were not significantly different from their age-matched controls on these two measures.										
Authors' Comments	It is possible that the exclusion of CKD participants with any major CNS-related effects may reduce generalizability of findings to the broader CKD population. Concomitantly, it is likely their inclusion into the study would have made even sharper differences between case and controls along measures of cognitive functioning. Serum measures of GFR and hemoglobin among the community-based control participants were not feasible. It is possible that there were some control group participants who had undetected compromised kidney functioning.										

<table>
<tr><td colspan="12">Umans J, Pliskin NH. Attention and Mental Processing Speed in Hemodialysis Patients. American Journal of Kidney Diseases 1998; Vol 32, No 5: 749-751</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td colspan="3">1</td><td colspan="3">2</td><td colspan="3">3</td><td colspan="2">4</td></tr>
<tr><td colspan="3">✓</td><td colspan="3"></td><td colspan="3">✓</td><td colspan="2"></td></tr>
<tr><td>Research Question</td><td colspan="11">What are the effects of hemodialysis on attention and mental processing?</td></tr>
<tr><td>Study Design</td><td colspan="11">Cohort-Control</td></tr>
<tr><td rowspan="4">Population</td><td colspan="2">Inclusion Criteria</td><td colspan="9">Subjects had to have a fractional urea clearance (Kt/V) greater than 1.0 and hematocrit of 30 or greater for each 6 months prior to study</td></tr>
<tr><td colspan="2">Exclusion Criteria</td><td colspan="9">None reported</td></tr>
<tr><td colspan="2">Study population Characteristics</td><td colspan="9">Measurement — Cases — Controls
Population (n) — 10 — 10
Age (years) — 61±6 — 62±10
Educations (years) — 12.4±3.8 — 11.6±1.0</td></tr>
<tr><td colspan="2">Generalizability to CMV drivers</td><td colspan="9">Unclear</td></tr>
<tr><td>Methods</td><td colspan="11">10 subjects and age and education matched controls participated in study after giving informed consent
All subjects with ESRD had been receiving hemodialysis (HD) 3 times weekly for 0.5 to 10 years without residual renal function
Subjects/Controls did not have history of hospitalization, unstable coronary vascular disease, cerebrovascular disease, depression, uncontrolled hypertension, active collagen vascular disease or vasculitis or use of glucocorticoids or medication with known effects on neuropsychological functioning prior to 6 months
Creatine clearance was estimated in controls b the method of Cockroft and Gault
6 tests were administered including the Stroop Color-Word test, trailmaking test, Digit Span, Paced Auditory Serial Addition test, Continuous Performance test, and the Gordon Diagnostic System Vigilance task
All study participants screened using Beck Depression Inventory to test for evident clinical depression
ESRD subjects tested on a single midweek nondialysis day to reduce the potential effects of varying uremia</td></tr>
<tr><td>Statistical Methods</td><td colspan="11">Data presented in the form of mean ± SD
T-test performed to analyze differences between group means
Criterion corrected for tests because of subtasks included to show significance p<0.05 (two sided) for 6 comparisons</td></tr>
<tr><td rowspan="2">Quality assessment</td><td rowspan="2">Study quality category: Moderate</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr>
<tr><td>No</td><td>S</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="11">Various neuropsychological test batteries performed to test for neurocognitive deficits
Beck Depression test administered to test for clinical depression</td></tr>
<tr><td>Results</td><td colspan="11">Study groups did not differ in age or education years
Groups did not include subjects with unrecognized depression (BDI scores 5.8± 3.3 for ESRD; 4.0±4.3 for controls
Refer to Table G-19 for complete details on testing results</td></tr>
<tr><td>Authors' Comments</td><td colspan="11">"It is unlikely that well-dialyzed patients with ESRD manifest significant uremic neurocognitive deficits in the functional spheres related to sustained attention or mental processing speed."</td></tr>
</table>

Table G-19. Attention and Mental Speed Measures

Test	ESRD	Control
Stroop Word	63.0 ± 12.6	76.1 ± 19.0
Stroop Color	47.8 ± 18.5	57.5 ± 15.7
Stroop Color/Word	23.3 ± 12.2	29.5 ± 12.7
Trails A	68.5 ± 48.1	67.4 ± 57.4
Trails B	313 ± 318	251 ± 252
PASAT 1	24.6 ± 6.9	21.2 ± 10.7
PASAT 2	23.6 ± 5.1	22.9 ± 11.6
PASAT 3	19.5 ± 5.2	21.0 ± 8.9
PASAT 4	17.6 ± 6.6	16.2 ± 8.3
Digit Span	10.6 ± 4.2	12.3 ± 4.1
CPT, no. of hits	308 ± 22	320 ± 6.0
CPT, no. of omissions	15.8 ± 22	3.6 ± 6.0
CPT, no. of commissions	5.3 ± 4.6	6.6 ± 3.4
CPT, RT (msec)	540 ± 74	474 ± 98
GDS, no. of hits	27.6 ± 3.4	26.1 ± 7.3
GDS, no. of omissions	2.4 ± 3.4	3.9 ± 7.3
GDS, no. of commissions	3.4 ± 5.0	1.9 ± 4.9
GDS, RT (msec)	46.9 ± 13.3	47.3 ± 13.1

NOTE. Values expressed as mean ± standard deviation.

Abbreviations: PASAT, Paced Auditory Serial Addition Test; CPT, Continuous Performance Test; GDS, Gordon Diagnostic System Vigilance Task; RT, reaction time.

Key Question 1: Sleep-related Evidence

Unruh M, Sanders M, Redline S, Piraino B, Umans J, Hammond T, Sharief I, Punjabi N, Newman A. Sleep apnea in patients on conventional thrice-weekly hemodialysis: comparison with matched controls from the Sleep Heart Health Study. J Am Soc Nephrol 2006; 17: 3503-09

Key Questions Addressed	1	2	3	4
	✓		✓	

Research Question: Association of sleep disordered breathing (SDB) and hemodialysis (HD)

Study Design: Cohort controlled

Population

Inclusion Criteria: Individuals undergoing in-center HD 3x/wk at one of 24 centers in Western PA; participated in studies performed from May 2004- September 2005. Controls had participated in the ongoing Sleep Heart Health Study (SHHS) from 2001-2002

Exclusion Criteria: Individuals with craniofacial abnormalities, age <45 yr or >90 yr, active malignancy, active infection (pneumonia), active coronary artery disease (i.e., MI, unstable angina) within the last 6 months, advanced cirrhosis, advanced dementia, or active alcohol abuse and those with refractory psychiatric disease; patients using continuous positive airway pressure, oral devices, or home oxygen therapy; pts with tracheostomy

Study population Characteristics

	Case	Control
n	46	137
Age (yr)	62.7±10.1	62.7±10.1
Gender Male	33 (71.7%)	98 (71.5%)
BMI (kg/m^2)	28.0±5.4	28.1±5.3
Lung disease	5 (10.8%)	23 (16.7%)
CVD	15 (32.6%)	17 (12.5%)
Diabetes	15 (32.6%)	12 (8.8%)
HD Treatment (median)	22 month (9-46 mo)	

Generalizability to CMV drivers: Unclear

Methods: All participants underwent polysomnography (PSG) overnight between 8:00 pm and 8:00 am. Medical history, sleep habits and subjective sleepiness information was obtained by interview, questionnaire and Epworth Sleepiness Scale, respectively.

Statistical Methods: Log-log transformation, conditional logistic regression, mixed-effects regression model, conditional logistic regression techniques

Quality Assessment

Study quality category: Moderate

1	2	3	4	5	6	7	8	9	10
No	S	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Relevant Outcomes Assessed: Rate of sleep disordered breathing

Results: Differences between groups include a higher rate of alcohol use in the SHHS sample, a higher systolic BP and a higher proportion of diabetes and CD in the HD group (Table G-20). An average mean single-pool Kt/V>1.2 or urea reduction rate >0.66 demonstrated adequate dosages of dialysis were being received. Results for sleep parameters are shown in Table G-21. Sleep time for the HD group was significantly shorter than the SHHS group (319.5±106.3 vs 378.9±67.3). Similar sleep efficiency was demonstrated (78.1±15.3 vs 81.3±10.4); and similar Stage 1 (5.0±3.4 vs 5.5±3.65) and Stage 2 sleep (57.6±14.3 vs 58.4±11.5). HD patients had significantly more Stage 3 to 4 sleep (23.4±12.2 vs 14.3±10.7, p<0.001); less REM sleep (13.6±8.2 vs 21.7±6.2, p<0.001); higher arousal index (25.1±14.6 vs 17.1±8.0); higher RDI (27.2±19.3, 15.2±4.9, p<0.001); and higher hypoxemic index (7.2±20.8 vs 1.84±8.4, p<0.001). Similar responses were shown for subjective sleepiness reported by ESS (9.0±4.7 vs 8.0±4.3). The HD sample had significantly higher odds of severe SDB (RDI>30; crude: odds ratio [OR] 3.49 [95% CI 1.5 to 7.9]; adjusted for history of diabetes and CVD: OR 4.02 [1.5 to 10.2].

Authors' Comments: HD patients had four-fold higher odds of having severe SDB. Generalizability of these results is supported by study recruitment from several HD units, adequate HD dosage and inclusion of a racially diverse sample.

Table G-20. Characteristics of Hemodialysis and Sleep Heart Health Study groups

Variable	HD Patients (n = 46)	Matched Controls (n = 137)	P^b
Age (yr)	62.7 ± 10.1	62.7 ± 10.1	NS
Male gender	33 (71.7)	98 (71.5)	NS
Race			
white	29 (63.0)	87 (63.5)	NS
black	16 (35.0)	47 (34.3)	NS
Native American	1 (2.0)	3 (2.2)	NS
BMI (kg/m^2)	28.0 ± 5.4	28.1 ± 5.3	NS
History of tobacco use	26 (56.5)	73 (53.3)	NS
Caffeinated beverage (servings/d; median [IQR])	2 (0 to 3)	2 (1 to 3)	NS
Alcohol (servings/wk; median [IQR])	0 (0 to 1)	1 (0 to 6)	<0.01
Benzodiazepine use	4 (8.7)	6 (4.4)	NS
Antidepressant use	6 (13.0)	13 (9.5)	NS
Systolic BP (mmHg)	137 ± 30.1	120.5 ± 14.9	<0.001
Diastolic BP (mmHg)	73.0 ± 15.0	72.7 ± 9.7	NS
Lung disease	5 (10.8)	23 (16.7)	NS
CVD	15 (32.6)	17 (12.5)	<0.01
Diabetes	15 (32.6)	12 (8.8)	<0.01

[a] Data are mean ±SD or n (%). BMI, body mass index; CVD, cardiovascular disease; HD, hemodialysis; IQR, interquartile range
[b] NS= P > 0.05.

Table G-21. Sleep parameters of Hemodialysis and Sleep Heart Health Study groups

Variable	HD Population (n = 46)	Matched Controls (n = 137)	P^b
Sleep time (min)	319.5 ± 106.3	378.9 ± 67.3	<0.001
Sleep efficiency (sleep time/total time in bed)	78.1 ± 15.3	81.3 ± 10.4	NS
Stage 1 sleep (%)[c]	5.0 ± 3.4	5.5 ± 3.65	NS
Stage 2 sleep (%)	57.6 ± 14.3	58.4 ± 11.5	NS
Stage 3 to 4 sleep (%)[c]	23.4 ± 12.2	14.3 ± 10.7	<0.001
REM sleep (%)	13.6 ± 8.2	21.7 ± 6.2	<0.001
Arousal index (arousals/h)[d]	25.1 ± 14.6	17.1 ± 8.0	<0.001
Respiratory disturbance index[d]	27.2 ± 19.3	15.2 ± 14.9	<0.001
Hypoxemic index[d,e]	7.2 ± 20.8	1.84 ± 8.4	<0.001
Lowest oxygen saturation, NREM[c]	83.6 ± 7.1	86.7 ± 5.3	<0.01
Lowest oxygen saturation, REM[c]	81.2 ± 9.7	85.9 ± 6.4	<0.001
Epworth Sleepiness Scale	9.0 ± 4.7	8.0 ± 4.3	NS

[a] Data are means±SD. NREM, non-rapid eye movement; REM, rapid eye movement.
[b] NS = p >0.05.
[c] Log-log transformation used for test of group differences.
[d] Log transformation used for test of group differences.
[e] The percentage of sleep time with an oxygen saturation of <90%.

Study Summary Tables for Key Question 3

Key Question 3: Neurocognitive Evidence

Altman P, Barnett ME, Fin WF. Cognitive function in Stage 5 chronic kidney disease patients on hemodialysis: No adverse effects of lanthanum carbonate compared with standard phosphate-binder therapy. Kidney International 2007; 71: 252-9.				
Key Questions Addressed (Indirect)	**1**	**2**	**3**	**4**
		✓		
Research Question	What are the effects of lanthanum carbonate or phosphate-binder therapy on cognitive functioning for individuals on hemodialysis with Stage 5 chronic kidney disease?			
Study Design	Randomized control trial (Multi-center)			
Population	**Inclusion Criteria**	None reported		
	Exclusion Criteria	Individuals excluded if: They had clinically significant abnormal lab values at screening, unless a result of Stage 5 CKD Individuals received psychotropic drugs who had been stabilized for ≤1 month Individuals were documented aluminum-related bone disease or dementia, calcium level below 7.9 mg/dl, evidence of previous gastrointestinal surgery or ongoing gastrointestinal disorders, levels of serum transaminases more than 3 times the upper limit of normal, life-threatening malignancy or multiple myeloma, known HIV positive status, exposure to an experimental drugs 30 days before screening Pregnant and or lactating Did not agree to used effective birth control methods for women of reproductive age		
	Study population Characteristics	**Measurement** / **Lanthanum** / **Standard Therapy** Population (n) / 170 / 181 Age (mean + SD) years / 54.4±15.6 / 56.5±14.1 Gender Male / 104 (58) / 109 (60) Female / 75 (42) / 72 (40) **Refer to** Table G-22 **for complete details**		
	Generalizability to CMV drivers	**Unclear**		
Methods	Cognitive function assessments conducted at 41 sites within the US for a subgroup of hemodialysis subjects form a 2 year randomized study which comprised of 3 phases: Screening and a 1-3 week washout period of previous phosphate binders 6 week dose titration period Long term maintenance of up to 2 years total participation Subjects randomized 1:1 to receive either treatments Lanthanum carbonate treatment started at a dose of 750 or 1500 mg/day; determined by investigator (dose could be titrated up to 3000 mg/day or down to 375 mg/day Individuals in the standard therapy group were able to switch or add other phoshate binders throughout the study but at the investigator's discretion Subjects were at least 18 years having received hemodialysis three times/weekly for Stage 5 CKD for 2 months prior to enrollment Investigator reviewed health, and compliance ability to meet study protocol Cognitive function assess using computer control tasks from the CDR cognitive assessment system Subjects received 2 training sessions during screening period; tests carried out at screening (pre-randomization/baseline), 3.5 months (Visit 9), 6 months (Visit 12), 12 months (Visit 15), 18 months (Visit 18) and 24 months (final visit) Subjects recruited for cognitive functioning before randomization into treatment groups to avoid potential bias First 3 tests looked at subject's attention span; last 2 exams looked at memory			

<table>
<tr><td>Statistical Methods</td><td colspan="14">Summary statistic calculated for measures and each time point by treatment
Mixed effects models for repeated measures used to look at differences from baseline
Random effects model included in model; baseline score used as covariate
Analysis conducted on intent-to-treat; defined as all subject randomized and had at least one post randomization phosphorus measurement</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Study quality</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Yes</td><td>NR</td><td>Yes</td><td>Yes</td><td>Yes</td><td>No</td><td>Yes</td><td>No</td><td>No</td><td>Yes</td><td>Yes</td><td>Yes</td><td>No</td></tr>
<tr><td rowspan="2">Category: Low</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td>No</td><td>No</td><td>No</td><td>NR</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">Psychological testing performed on subjects to test for cognitive functioning
Amounts of drug exposure observed and recorded</td></tr>
<tr><td>Results</td><td colspan="14">Median plasma levels for lanthanum level in all subjects at screening was 0.0 ng/ml (range: 0.0-0.4 ng/ml); randomized lanthanum carbonate group rose to 0.3 ng/ml by week 7 and remained constant afterwards
Randomized standard therapy group's mean serum lanthanum level remained at 0.0 ng/ml (range: 0.0-2.7 ng/ml) throughout the entire study with the exception of month 18 when median level was 0.1 ng/ml (range: 0.0-0.2 ng/ml)
Psychotic drugs used by 85 (47%) subjects who were randomized to the lanthanum carbonate group and 38% randomized to the standard therapy group
Differences in cognitive function for both treatment arms recorded at baseline in Table G-23
Vigilance testing showed a significant treatment-by-visit interaction (p=0.027; Table G-24, Figure G-4)
No significant difference between the declines for Choice Reaction time for both treatment groups, p=0.17; Figure G-5; significance shown in treatment-by-visit-interaction, p=0.035
Response time was greater in standard therapy group with an overall treatment effect favoring lanthanum carbonate (p=0.02). Refer to Figure G-6 for complete detail
Mixed effects model results shown in Table G-24
Table G-25 includes lists of CDR assessments performed for study subjects</td></tr>
<tr><td>Authors' Comments</td><td colspan="14">"Hemodialysis patients who were treated with lanthanum carbonate and standard phosphate binders showed deterioration in cognitive function during 2 years follow-up. This deterioration was marked compared with normal aging and was independent of the phoshate-binder therapy that was used"</td></tr>
</table>

Table G-22. Baseline characteristics and renal history

Characteristic	Lanthanum carbonate (*n*=179)	Standard therapy (*n*=181)
Age, mean ± s.d. (years)	54.4 ± 15.6	56.5 ± 14.1
Gender, n (%)		
Male	104 (58)	109 (60)
Female	75 (42)	72 (40)
Race, n (%)		
Caucasian	98 (55)	87 (48)
Black	68 (38)	73 (40)
Hispanic	10 (6)	15 (8)
Asian/Pacific	0	4 (2)
Native American	2 (1)	1 (1)
Other	1 (1)	1 (1)
Weight, mean ± s.d. (kg)	80.2 ± 22.4	80.8 ± 19.5
Height, mean ± s.d. (cm)	169.9 ± 11.4	171.7 ± 10.9
Primary renal diagnosis, n (%)		
Diabetes	52 (29)	62 (34)
Hypertension	59 (33)	44 (24)
Glomerulonephritis	20 (11)	26 (14)
Cystic kidney disease	10 (6)	10 (6)
Urologic disease	1 (1)	4 (2)
Unknown cause	5 (3)	3 (2)
Other known cause	32 (18)	32 (18)
Previous kidney transplant, n (%)		
No	150 (84)	1678 (92)
Yes	29 (16)	14 (8)
Duration on hemodialysis (years)		
Median	2.82	2.37
Range	0.4–19.4	0.4–21.8
Previous treatment, n (%)		
Calcium acetate	76 (43)	75 (41)
Calcium carbonate	50 (28)	60 (33)
Not listed	1 (1)	3 (2)
Other therapy	7 (4)	6 (3)
Sevelamer hydrochloride	44 (25)	37 (20)

Table G-23. Baseline scores on the Cognitive Drug Research tasks

	Lanthanum carbonate (n=174)	Standard therapy (n=178)
Simple Reaction Time (ms)		
Mean	378.0	423.1
95% CI	362.2, 397.7	393.6, 452.5
Digit Vigilance – targets detected (%)		
Mean	92.7	90.7
95% CI	91.2, 94.2	88.7, 92.7
Digit Vigilance – response time (ms)		
Mean	486.2	503.5
95% CI	475.4, 497.1	491.6, 515.4
Digit Vigilance – false alarms (#)		
Mean	1.90	2.12
95% CI	1.54, 2.25	1.70, 2.55
Choice Reaction Time – accuracy (%)		
Mean	96.6	96.2
95% CI	95.9, 97.2	95.4, 97.0
Choice Reaction Time – response time (ms)		
Mean	600.2	641.8
95% CI	579.9, 620.5	614.4, 669.2
Numeric Working Memory – sensitivity index[a]		
Mean	0.88	0.83
95% CI	0.85, 0.90	0.80, 0.86
Numeric Working Memory – response time (ms)		
Mean	1067	1137
95% CI	1011, 1122	1073, 1201
Picture Recognition – sensitivity index		
Mean	0.59	0.54
95% CI	0.55, 0.62	0.50, 0.57
Picture Recognition – response time (ms)		
Mean	1377	1461
95% CI	1301, 1452	1380, 1541

CDR, Cognitive Drug Research; CI, confidence interval; SI, sensitivity index.
[a]SI combines the ability to identify previously presented items correctly and to reject those that were not previously presented. The score represents the overall ability of the patient to recognize (or be sensitive to) the task information (1=perfect discrimination; 0=chance performance).[32]

Table G-24. P-values from the mixed effect model

Parameter	Treatment[a]	Visit[b]	Treatment-by-Visit Interaction[c]
Simple Reaction Time (ms)	0.4520	0.0024*	0.2725
Digit Vigilance – targets detected (%)	0.0275*	0.0141*	0.0269*
Digit Vigilance – response time (ms)	0.6949	0.0001*	0.4772
Choice Reaction Time – response time (ms)	0.1681	0.0001*	0.0352*
Numeric Working Memory – sensitivity index (SI)	0.1288	0.0886	0.6424
Numeric Working Memory – response time (ms)	0.0243*	0.1169	0.8846
Picture Recognition – SI	0.2911	0.0372*	0.2625
Picture Recognition – response time (ms)	0.7612	0.8701	0.1646

*Statistically significant.
[a]A significant treatment effect indicates a difference in overall effect between the two groups.
[b]A significant visit effect indicates an overall change (deterioration in this case) over time.
[c]A significant treatment by visit interaction indicates a different rate of decline between the two treatment groups.

Table G-25. List of Cognitive Drug Research Assessments

Task	Description	Major measure	Supporting measure[a]
Attentional Tasks:			
Simple Reaction Time	The patient was instructed to press the 'YES' response button as quickly as possible every time the word 'YES' was presented on the monitor. Thirty stimuli were presented at varying interstimulus intervals.	Response time (ms)	
Digit Vigilance	A target digit was randomly selected and constantly displayed to the right of the monitor screen. A series of digits was presented in the center of the screen at the rate of 150 per minute, and the patient was required to press the 'YES' button as quickly as possible every time the digit in the series matched the target digit. In total, 450 digits, including 45 targets, were presented over 3 min.	Response time (ms) Targets detected (%)	False alarms (#)
Choice Reaction Time	Either the word 'NO' or the word 'YES' was presented on the monitor and the patient was instructed to press the corresponding button as quickly as possible. Thirty trials were chosen randomly with equal probability, and were presented at varying interstimulus intervals.	Response time (ms)	Accuracy (%)
Working Memory Task:			
Numeric Working Memory	A series of five digits was presented for the patient to remember, followed by a series of 30 probe digits. For each digit, the patient indicated whether or not they recognized it as being from the original series by pressing the 'YES' or 'NO' button as appropriate.	Sensitivity index (SI)[b] Response time (ms)	
Episodic Secondary Memory Task:			
Picture Recognition	Before the Simple Reaction Time test, a series of 20 pictures was presented on the monitor at the rate of one every 3 seconds for the patient to remember. In the Picture Recognition test, the original pictures, plus 20 distracter pictures, were presented one at a time in a randomized order. For each picture, the patient indicated whether or not they recognized it as being from the original series by pressing the 'YES' or 'NO' button as appropriate.	Sensitivity index (SI)[b] Response time (ms)	

[a]Analysis of covariance was not carried out on the supporting measures.
[b]SI combines the ability to identify previously presented items correctly and to reject those that were not previously presented. The score represents the overall ability of the patient to recognize (or be sensitive to) the task information (1=perfect discrimination; 0=chance performance).[32]

Figure G-4. Digit Vigilance Task-target detected (%) (least-squares means±95% CI from mixed effect model).

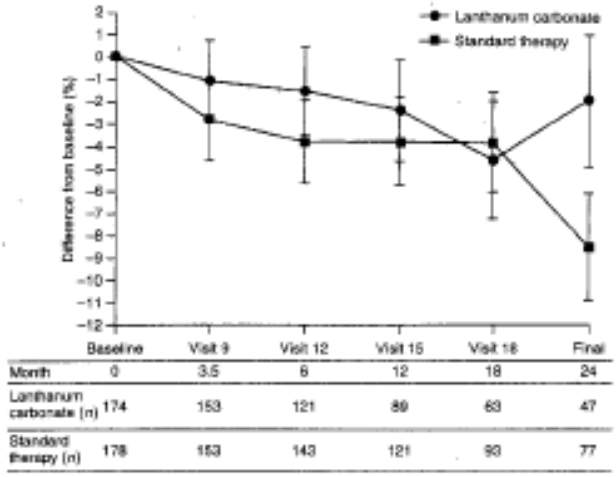
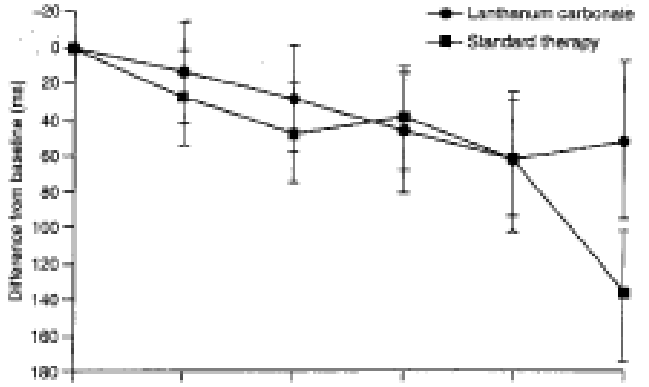
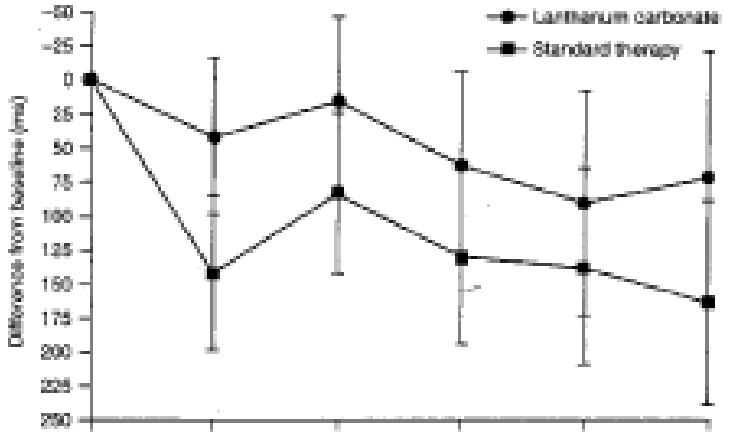


Figure G-5. Choice Reaction Time-response time (ms) (least-squares means±95% CI from repeated mixed effect model).



Month	0	3.5	6	12	18	24
Lanthanum carbonate (n)	174	153	121	89	63	47
Standard therapy (n)	178	153	143	121	93	77

Figure G-6. Numeric Working Memory-response time (ms) (least-squares means±95% CI from mixed effect model).



Month	0	3.5	6	12	18	24
Lanthanum carbonate (n)	174	153	121	89	63	47
Standard therapy (n)	178	153	143	121	93	77

<table>
<tr><td colspan="12">Buoncristiani, U., Alberti, A., Gubbiotti, G., Mazzotta, G., Gallai, V., Quintaliani, G., Gaburri, M. Better Preservation of Cognitive Faculty in Continuous Ambulatory Peritoneal Dialysis. Peritoneal Dialysis International; 13, Supplement 2: S202-S205, 1992.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td colspan="3">1</td><td colspan="3">2</td><td colspan="3">3</td><td colspan="2">4</td></tr>
<tr><td colspan="3"></td><td colspan="3"></td><td colspan="3">✓</td><td colspan="2"></td></tr>
<tr><td>Research Question</td><td colspan="11">Is there a difference in cognitive functioning between patients on hemodialysis (HD) and those on continuous ambulatory peritoneal dialysis (CAPD)?</td></tr>
<tr><td>Study Design</td><td colspan="11">Cohort, pre-post</td></tr>
<tr><td rowspan="3">Population</td><td>Inclusion Criteria</td><td colspan="10">Cases: Patients diagnosed with uremic neuropathy end-stage renal failure and in need of dialysis. Patients were grouped according to the type dialysis treatment. Group I: Received CAPD treatment for at least 6 months prior to testing. Group II: Received HD treatment for at least 6 months prior to testing.
Control: Healthy respondents with no diagnosed kidney disease matched on age for Groups I and II.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="10">None reported.</td></tr>
<tr><td>Study population Characteristics</td><td colspan="10">Measure Group I Group II Controls
Population (n) 22 15 NR
Age ± y 60 ± 11 59 ± 11 NR
Range y 28-77 31-72 NR
Male 50% NR NR</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="10">Unclear</td></tr>
<tr><td>Methods</td><td colspan="11">Cases and Controls were administered a battery of four tests designed to measure cognitive-neurological functioning:
ERP (event-related potentials); an electro-physiological test where subjects were fitted with electrodes and fed 160 audio signals and were instructed to alert the researcher with an electronic button when they heard a tone that was rare in Hz. The test was designed to capture any change or deviation from normative electrical activity in short-term memory processing.
Digit Span: Performance test to measure short-term memory and concentration'
Number Connection: Performance test to measure response time.
Mini Mental Test: Not described except as part of awake-time neural functioning
HD patients (given dialysis 3x per week) were given the test battery before their dialysis treatment and no later than hours after the treatment was completed (pre-post measures).
Because CAPD is continuous treatment, no pre-post measures were performed.</td></tr>
<tr><td>Statistical Methods</td><td colspan="11">Statistical analyses were performed using Student's t-test for the paired and unpaired measured.
ANOVA was selected for the three-group analyses.
Alpha level for significance was not reported; assumed to be a two-tailed test of significance at $p < 0.05$</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Cohort Comparison. Quality Rating: Low</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr>
<tr><td>No</td><td>No</td><td>Yes</td><td>No</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td></tr>
<tr><td rowspan="2">Pre-Post Comparison. Quality Rating: Moderate</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td></tr>
<tr><td>Yes</td><td>No</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="11">Normal/Abnormal ERP results (as measured by latency of responses)
Performance tests results for Digit Span, Number Connection and Mini Mental Test
HD patients results pre-and post-dialysis session.</td></tr>
<tr><td>Results</td><td colspan="11">Prior to dialysis treatment, HD patients showed abnormal brain electrical activity on the ERP test, evidenced by significantly longer latency of response from auditory signal to response (> 100 msec.).
After dialysis treatment, HD patients responses were equivalent to those of CAPD patients and Controls.</td></tr>
<tr><td>Authors' Comments</td><td colspan="11">"These results support the conclusion that HD is able to restore a normal cognitive faculty only transiently in the postdialytic phase, while CAPD maintains this important function steadily close to the normal range, thus being clearly better than HD."</td></tr>
</table>

<table>
<tr><td colspan="12">Evans J, Wagner C, Welch J. Cognitive status in hemodialysis as a function of fluid adherence. Renal Failure 2004; 26: 575-581</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="2">2</td><td colspan="2">3</td><td colspan="2">4</td><td colspan="4">5</td></tr>
<tr><td>✓</td><td colspan="2"></td><td colspan="2">✓</td><td colspan="2"></td><td colspan="4"></td></tr>
<tr><td>Research Question</td><td colspan="11">Influence of adherence to fluid intake on cognitive functioning for a group of hemodialysis (HD) patients, and hemodialysis patients compared with normative data</td></tr>
<tr><td>Study Design</td><td colspan="11">Historical Cohort, Cohort</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="10">Individuals aged 18+ years receiving HD as a primary treatment for ESRD; ability to speak and understand English</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="10">Presence of a psychiatric disorder including clinical depression; living in an extended-care facility; receiving outpatient hemodialysis on a temporary basis following a peritoneal dialysis (PD) complication or transplant rejection; recently began HD therapy</td></tr>
<tr><td>Study population Characteristics</td><td colspan="10"><table><tr><td><u>Variable</u></td><td><u>Adherent</u></td><td><u>Nonadherent</u></td></tr><tr><td>n</td><td>47</td><td>100</td></tr><tr><td>Age: (yrs.) mean ±SD</td><td>55.7±14.2</td><td>53.9±14.0</td></tr><tr><td>Gender M/F</td><td>38% M</td><td>66% M</td></tr><tr><td>Duration on dialysis (yrs)</td><td>6.25±7.3</td><td>4.3±3.6</td></tr><tr><td>Ethnicity (% black)</td><td>66%</td><td>53%</td></tr></table></td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="10">Unclear</td></tr>
<tr><td>Methods</td><td colspan="11">Patients were recruited from 3 dialysis clinics. Measurements of cognitive function were assessed by Cognistat, a 10 to 20 minute screening test to evaluate cognitive dysfunction in multiple, independent domains. Testing was undertaken during the first hour of dialysis.</td></tr>
<tr><td>Statistical Methods</td><td colspan="11">T tests, chi-square analyses, inferential analyses</td></tr>
<tr><td rowspan="2">Quality assessment</td><td>Study quality: Cohort</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr>
<tr><td>Score: Low</td><td>No</td><td>S</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="11">Cognitive function</td></tr>
<tr><td>Results</td><td colspan="11">Results for performance on Cognistat indicate rates of impairment ranging from 2.7% (orientation) to 54% (memory) for the entire sample size (Figure G-1). While slight impairment was demonstrated on tests for orientation, comprehension and naming, testing for memory, construction and similarities showed greatest impairment. A comparison of Cognistat scores of HD patients to standardization samples of the Cognistat demonstrated their performance to be most similar to a sample of healthy adults (average age of 50.8 yrs) and superior on all subscales versus a group of neurosurgical patients (average age of 54.2 yrs)(Table G-6). Scores for HD patients were similar to healthy adults with the exception of a lower score on the memory subscale (8.6±3.0 vs 11.5±0.7). With the exception of a significantly better performance by nonadherent pts on scores for calculation (p<.05), there was no significant differences on subscale performance in relation to fluid adherence. (Figure G-2).</td></tr>
<tr><td>Authors' Comments</td><td colspan="11">No direct relationship was found for fluid adherence and cognitive functioning.</td></tr>
</table>

Figure G-7. Rate of Impairment on Cognistat Score (%)

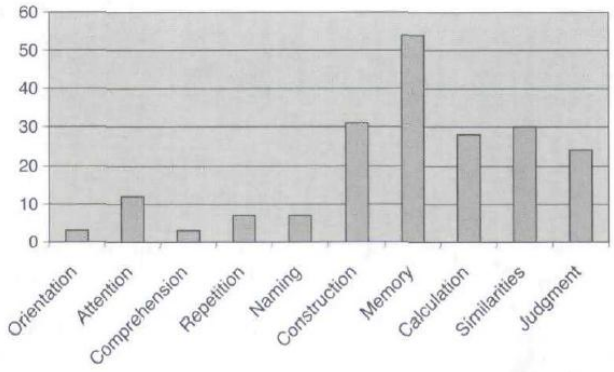
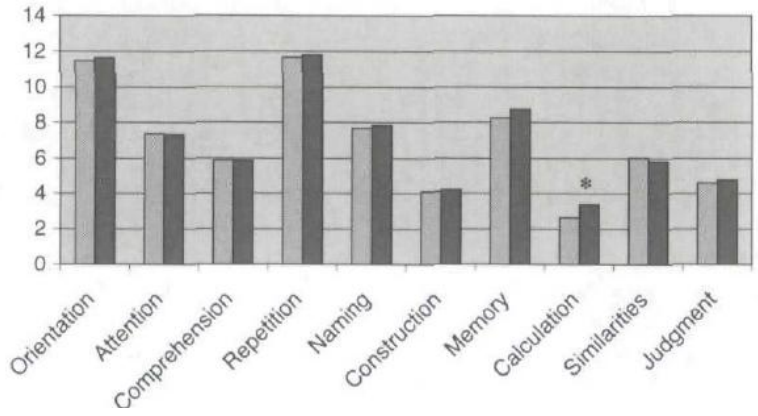


Table G-26. Comparison of Cognistat Scores

Cognistat subscale	Hemodialysis patients mean (SD)	Standardization sample mean (SD)	Neurosurgical sample mean (SD)
Orientation	11.6 (0.7)	12.0 (0.0)	10.5 (2.6)
Attention	7.3 (1.3)	7.1 (1.2)	6.3 (2.4)
Comprehension	5.9 (0.4)	6.0 (0.2)	5.0 (1.5)
Repetition	11.8 (0.9)	12.5 (0.8)	11.1 (2.9)
Naming	7.8 (0.6)	8.5 (0.7)	7.1 (2.1)
Construction	4.2 (2.0)	5.0 (0.4)	3.6 (1.8)
Memory*	8.6 (3.0)	11.5 (0.7)	6.3 (3.6)
Calculation	3.2 (1.4)	3.8 (0.6)	3.0 (1.5)
Similarities	5.9 (2.4)	6.1 (1.3)	4.3 (2.5)
Judgment	4.7 (1.4)	5.1 (0.5)	4.9 (1.3)

* p <0.1

Figure G-8. Cognistat Scores by Level of Fluid Adherence



† adherent; ■ non-adherent. * = *p* <.05

Griva K, Newman S, Harrison M, Hankins M, Davenport A, Hansraj S, Thompson D. Acute neuropsychological changes in hemodialysis and peritoneal dialysis patients. Health Psychology 2003; 22: 570-578

Key Questions Addressed	1	2	3	4
			✓	

Research Question: Neuropsychological function of hemodialysis patients

Study Design: Cohort, pre-post

Population

Inclusion Criteria: Individuals recruited from renal units at 2 hospital sites; aged 18+ years; currently stable (defined as not being acutely ill or hospitalized at the time of assessment); fluent in English; minimum of 3 months on respective treatment and dialysis technique

Exclusion Criteria: No history or clinically evident cerebrovascular disease as reflected by new, transient, or fixed neurological deficits; no major visual or hearing impairments or other sensory or motor impairments that may restrict them from completing study assessments; absence of acute or chronic psychosis; evident depression, severe learning disabilities; dementia;

Study population Characteristics

Variable	Hemodialysis (HD)	Controls (Peritoneal dialysis (PD))
n	77	68
Hospital Hemodialysis	52	
Home Hemodialysis	25	
Continuous Ambulatory Peritoneal Dialysis		45
Automated Peritoneal Dialysis		23
Age: (yrs.) mean ±SD	48.22±14.92	52.26±13.26
Gender M/F (%)	57.1/42.9	73.5/26.5
Ethnicity	68.8% Caucasian	58.8% Caucasian
Dialysis (time in months)	52.41±55.03	20.75±22.37
Renal replacement therapy (mos)	96.35±83.18	30.26±40.82
ESRD severity	10.57±9.13	11.81±9.87

Generalizability to CMV drivers: Unclear

Methods: Patients were all evaluated for adequate dialysis treatments levels. Two neuropsychological testing assessments included Trail Makin Tests A and B (TMT) (lower scores indicate better cognitive function); Symbol Digit Modalities Test (SDMT, both written and oral); Rey Auditory Verbal Learning Test (RAVLT); Benton Visual Retention Test (BVRT); and Grooved Pegboard (GP)(higher scores indicate worse performance) were conducted over a 24-hour period. Assessments were administered 2 hour prior to dialysis (T1) and 24 hr after the end of their last dialysis session (T2).

Statistical Methods: Independent t tests, chi-square tests, ANCOVA, hierarchical multiple regressions, residualized change scores

Quality assessment

Cohort comparison study quality: Hemodialysis Rating: Low	1	2	3	4	5	6	7	8	9	10
	Yes	NR	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Cohort comparison study quality: Peritoneal dialysis Rating: Moderate	1	2	3	4	5	6	7	8	9	10
	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Pre-post study quality rating Rating: Moderate	1	2	3	4	5	6	7	8	9	10	11
	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes

Relevant Outcomes: Post-dialysis change in neuropsychological performance

Assessed	
Results	Baseline characteristics are shown in Table G-27. Results for neuropsychological performance are shown in Table G-28. In a series of repeated measures ANCOVA (covariates: fatigue, anxiety, dialysis duration, and diabetic status) comparing the neuropsychological performance (NP) of the hemodialysis and peritoneal dialysis groups over time revealed a consistent pattern of results. Findings included both treatments averaged over time result in equivalent cognitive functioning; improved neuropsychological performance in the combined dialysis sample at T2 (second dialysis administration). Results for Group X Time interaction effect demonstrated significance for NP scores in 9/10 tests. While NP for HD patients improved significantly 24 hours post-dialysis, test performance for PD patients remained largely unchanged from T1 to T2 . Slight improvements were only demonstrated for TMT-A, SDMT-W and SDMT-O.
Authors' Comments	Neuropsychological performance for HD patients improved significantly 24 hours post-dialysis while performance for PD patients remained mostly consistent. Investigators concluded that PD patients had more stable physiological functioning and any slight improvement in test performance resulted from learning effects.

Table G-27. Baseline Characteristics

	HD (n = 77)			PD (n = 68)				
Variable	*M*	*SD*	%	*M*	*SD*	%	$t(144)$	$\chi^2(144)$
Age (years)	48.22	14.92		52.26	13.26		−1.70	
Gender (female)			42.9			26.5		4.25*
Ethnicity (White)			68.8			58.8		3.29
Married			57.1			70.1		2.81
Employed			36.4			35.1		0.17
Education (years)	12.26	5.69		12.49	5.11		−0.26	
DL (time in months)	52.41	55.03		20.75	22.37		4.63**	
RRT (time in months)	96.35	83.18		30.26	40.82		6.18**	
ESRD severity	10.57	9.13		11.81	9.87		−0.79	
Kt/V[a]	1.69	0.24		1.94	0.42			
Urea reduction ratio	0.65	0.07						
Previous transplant			94.1			50.6		33.10**
On transplant list			89.6			89.7		0.00
Diabetes			7.8			27.9		10.20**
Hypertension			94.8			88.2		2.05
Heart disease			39.0			41.2		0.07
Primary cause of ESRD								
Glumeronephritis			23.4			2.9		***[b]
APKD			13.0			14.7		0.09
Reflux			9.1			10.3		0.06
Diabetes			6.5			16.2		3.44
Hypertension			5.2			16.2		3.58

Note: HD=hemodialysis; PD=peritoneal dialysis; DL+dialysis;
RRT=renal replacement therapy; Kt/V = K is the total urea clearance rate,
t is the number of minutes of dialysis, and V is the urea distribution within
the patients; ESRD=end-stage renal disease; APKD= adult polysystic kidney disease.
[a] Absolute values are not directly comparable between HD and PD patients.
[b] Fisher's exact test.
* p <.05 ** p<.01 *** p<.001

Table G-28. Neuropsychological Testing Scores (T1 and T2)

	Hemodialysis		Peritoneal dialysis		
Measure	Time 1	Time 2	Time 1	Time 2	*F*(6, 133)
TMT–A[a]					
M	53.73	45.13	50.49	46.60	4.93*
SD	37.32	32.34	25.98	26.35	
TMT–B[a]					
M	97.92	90.02	99.32	99.96	7.82**
SD	51.72	51.72	44.74	46.74	
SDMT–W[b]					
M	40.92	47.10	41.31	44.73	5.24*
SD	12.96	15.20	12.66	14.56	
SDMT–O[b]					
M	45.82	52.10	44.91	48.61	4.70*
SD	14.22	16.58	13.24	15.87	
RAVLT–T					
M	39.36	43.53	38.65	39.16	14.29***
SD	11.94	11.78	9.20	8.77	
RAVLT–D					
M	2.35	2.64	2.75	3.03	0.40
SD	1.70	2.09	2.20	1.61	
BVRT–C[b]					
M	5.08	5.97	4.75	4.97	4.17*
SD	2.30	2.31	1.98	1.74	
BVRT–E[c]					
M	8.64	6.61	8.47	7.82	7.38**
SD	5.46	5.30	4.51	3.85	
GP–DOM[a]					
M	88.66	85.12	93.65	91.95	6.69*
SD	29.78	28.81	34.28	32.16	
GP–NDOM[a]					
M	100.19	95.40	104.61	103.25	10.19**
SD	34.59	34.31	43.64	39.71	

Note: The F test denotes the Group x Time interaction effect for the 2 x 2 analysis of covariance. TMT-A = Trail Making Test, Form A; TMT-B = Trail Making Test, Form B; SDTM-W = Symbol Digit Modality Test written administration; SDMT-O = Symbol Digit Modality test oral administration; RAVLT-T = Rey Auditory Verbal Learning Test total word recall after Trials 1-5; RAVLT-D=Rey Auditory Verbal Learning Test Test drop in retention from Trials 5-7; BVRT-C=Benton Visual Retention Test number of correct reproductions; BVRT-E=Benton Visual Retention Test number of reproduction errors; GP-DOM=Grooved Pegboard dominant hand; GP=NDOM=Grooved Pegboard nondominant hand.

[a] Time to completion in seconds. [b] Number correct. [c] Number of errors.

* p<.05. **p<.01. ***P<.001.

Hart R, Pederson J, Czerwinski A, Adams R. Chronic renal failure, dialysis, and neuropsychological function. Journal of Clinical Neuropsychology 1983; 5: 301-312

Key Questions Addressed	1	2	3	4
	✓		✓	

Research Question: Determine influence of dialysis on neuropsychological function

Study Design: Cohort

Population

Inclusion Criteria: 62 patients aged 17-62 years; hemodialysis patients attending dialysis units at Oklahoma Memorial Hospital, the VA Hospital and Midwest Dialysis Center in Oklahoma City, OK; nondialyzed patients attended outpatient renal clinics at Oklahoma Memorial and VA Hospitals; controls attended outpatient clinics at O'Donahue Rehabilitation Center, an outpatient pain clinic at Oklahoma Memorial Hospital, an outpatient therapy group for individuals with physical disabilities at the VA Hospital, and the Paralyzed VA in Oklahoma. Two of the controls were inpatients (Neurology, Rehabilitation Medicine) at the VA Hospital.

Exclusion Criteria: Individuals with sensory or motor disabilities which would adversely affect their performance on tasks

Study population Characteristics

Variable	Hemodialysis Pts	Nondialyzed Renal Pts	Control
N	24	18	20
Age (yrs) mean±SD	40.3±13.1	43.0±11.9	40.5±11.3
Education (yrs) mean	12.1±12.1	12.5±2.6	12.3±2.0
Gender M/F	12/12	11/7	16/4
Ethnicity	75% Caucasian	67% Caucasian	85% Caucasian

Duration Tx mean±SD 2.7±2.7 yrs
Length of time attending clinic (mean±SD): 5.1±5.5 yrs
Duration of chronic physical disabilities (mean±SD): 9.6±10.9 yrs

Generalizability to CMV drivers: Unclear

Methods: Diagnosis of dialysis and renal patients are listed in the table below. Patient assessments included psychometric measures of attention, recent memory and new learning, visuomotor speed and accuracy. See below for a test listing. Study participants were tested on various days; dialysis pts on a day they were not scheduled for dialysis, renal pts on a clinic visit or prior to hospital discharge, and controls were seen as outpatients.

Statistical Methods: Multivariate analysis of variance, one-way analysis of variance, Duncan's Multiple Range Test, Pearson correlation coefficients

Quality Assessment

Internal Validity Category: Low	1	2	3	4	5	6	7	8	9	10
	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Relevant Outcomes Assessed: Neuropsychological function

Results: Test performance scores are shown in An overall effect of Group, *F* (28, 92) = 2.1, P<.01 was found in a multivariate analysis of variance of the 14 measures of cognitive and perceptual-motor function. A one-way analysis of variance done for each individual measure indicated groups differed on 9/14 measures. Impaired performance by renal pts on all nine of these measures versus controls or to both controls and dialysis pts was measured in an individual comparison using Duncan's Multiple Range Test (p<0.5). Compared to controls, dialysis pts were only impaired on Visual Reproduction and performed worse than controls on 9/13 remaining measures. No significant correlations were found among dialysis pts for years of dialysis treatment and performance on any measure. In contrast, both blood urea nitrogen (BUN) and serum creatinine levels for renal clinic pts were highly correlated with performance on several tests. BUN and serum creatinine levels of renal pts were significantly correlated (r =.72, p<.0007).. In a comparison of "all renal pts" versus renal pts attending clinics for <6 months, data demonstrated that a shorter treatment time predicted less efficient performance (.Investigators concluded that the onset of treatment at a renal clinic seems to have beneficial effects on psychomotor efficiency and mental alertness.

Authors' Comments: "The mild impairment n dialysis patients do not seem to be directly attributable to dialysis treatments. Rather, the onset of hemodialysis appears to have beneficial effects on neuropsychological function."

Table G-29. Diagnoses of Dialysis and Renal Clinic Patients

	Dialysis		Renal Clinic	
	$n = 24$		$n = 18$	
Diagnosis	n	+biopsy	n	+biopsy
Hereditary Nephritis	3	2	1	1
Polycystic Kidney Disease	3	–	3	–
Chronic Interstitial Nephritis	2	2	2	–
Chronic Interstitial Nephritis: Hypertension	4	2	2	–
Chronic Interstitial Nephritis: Obstruction	1	–	–	–
Chronic Interstitial Nephritis due to obstruction and infection	1	–	–	–
Glomerulonephritis	–	–	1	–
Glomerulonephritis - membrane proliferation	1	1	2	2
Glomerulonephritis, crescentic	1	1	1	1
Glomerulonephritis: Wegners Granuloma	1	1	–	–
Glomerulonephritis, Segroental Sclerosing	–	–	1	1
Lupus Nephritis	2	2	–	–
Glomerulosclerosis	1	1	–	–
Diabetic Glomerulosclerosis	4	2	5	1

Table G-30. Study Assessments

Test	Description
Mental Control	
Digit Span	
Logical Memory	
Visual Reproduction	
From the Wechsler Memory Scale	
Trial Making Tests (Parts A and B)	
WAIS Digit Symbol	
Digit Vigilance Test of the Rennick Repeatable Battery	
Purdue Pegboard (dominant hand)	
Free verbal learning task	Immediately recall 20 lists of common words. Each list was composed of 12 words presented auditory at a rate of 1 ½ s/word. All words were classified as A in the Thorndike-Lorge (1944) word count
Facial recognition memory task	48 faces were presented for 5 s each. 48 forced-choice recognition trials followed in which the original stimulus had to be chosen over a distracter.
Symbol digit paired-associate learning task	Subjects were to learn a list composed of eight relatively unfamiliar symbols, each paired with a one-digit number. For 3 s, subjects are shown each pair. Subjects are then shown the symbol and asked to retrieve the corresponding number. Each response was followed by correctly paired symbol-digit for 3 s. Four test trials were performed.

Table G-31. Test Performance

Measure	Dialysis $n=24$ M	Dialysis $n=24$ SD	Renal Clinic $n=18$ M	Renal Clinic $n=18$ SD	Controls $n=20$ M	Controls $n=20$ SD	F	p
Age	40.3	13.1	43.0	11.9	40.5	11.3	<1	NS
Education	12.1	2.7	12.5	2.6	12.3	2.0	<1	NS
Beck Depression	12.0	6.2	9.2	6.3	14.1	8.5	2.33	NS
Mental Control	6.5	1.9	6.0	2.1	6.5	1.9	<1	NS
Digit Span Forward	5.8	1.0	6.0	1.3	5.9	1.4	<1	NS
Digit Span Backward	4.7	1.1	4.1	0.8	4.6	1.2	1.92	NS
Digit Vigilance-Time	203.3	38.2	270.2**	99.9	201.0	43.6	7.27	.002
Digit Vigilance-Error	3.6	3.3	8.2**	11.1	2.8	3.4	3.76	.03
Trails A	31.2	10.1	46.8**	21.5	35.3	13.1	5.69	.006
Trails B	92.8	47.4	146.7**	74.5	81.9	22.9	8.59	.001
Digit Symbol	47.0	8.9	40.8*	12.2	48.7	10.5	3.01	.06
Logical Memory	8.7	2.9	7.0*	2.7	10.2	2.9	6.02	.005
Visual Reproduction	8.3*	3.0	6.8*	3.2	10.2	2.4	6.62	.003
Word List	89.0	20.2	87.7	16.4	87.3	8.6	<1	NS
Facial Memory	37.3	5.2	33.5**	6.0	38.8	5.0	4.74	.02
Symbol-Digit Paired Associates	21.8	8.3	19.4	7.5	23.0	6.6	1.06	NS
Purdue Pegboard (D)	11.8	2.5	11.4*	2.2	13.1	1.6	3.15	.05

* $p<0.05$ compared to controls, Duncan's Multiple Range Test

** $p<.05$ compared to both dialysis patients and controls, Duncan's Multiple Range Test

Table G-32. Correlations between BUN and Creatinine with Test Performance in Renal Clinic Patients

Measure	r with BUN	p	r with Cr	p
Digit Vigilance Time	.68	.002	.51	.03
Digit Symbol	−.56	.02	−.41	.06
Purdue Pegboard (D)	−.53	.02	−.40	.06
Digit Span Forward	−.45	.05	−.18	.25
Facial Memory	−.23	.20	−.35	.09

Table G-33. Intercorrelation (r) Among Test Scores in Renal Clinic Pts

Intercorrelation (r) Among Test Scores in Renal Clinic Patients

	Digit Vigilance Time	Trail A	Trail B	Digit Symbol	Purdue Pegboard
Digit Vigilance Time	-----				
Trail A	.73 $p<.001$	-----			
Trail B	<.57 $p<.02$	.74 $p<.0005$	-----		
Digit Symbol	-.67 $p<.003$	-.79 $p<.0001$	-.83 $p<.0001$	-----	
Purdue Pegboard	-.60 $p<.009$	-.70 $p<.002$	-.82 $p<.0001$	.86 $p<.0001$	-----

Table G-34. Mean Performance Ratings and Age-Corrected Scaled Scores

Measure	Controls $n = 20$	Dialysis Patients $n = 24$	All Renal Clinic Patients $n = 18$	Renal Clinic Patients Attending Clinic > 6 mo. $n = 13$
Logical Memory[a]	1.9	2.7	3.5	3.2
Visual Reproduction[a]	1.3	2.0	2.7	2.4
Trail Making Test, Part A[b]	1.6	1.4	2.3	1.8
Trail Making Test, Part B[b]	1.2	1.4	2.6	1.9
Digit Vigilance[c]	1.7	1.8	2.4	2.2
Digit Symbol[d]	9.2	8.7	7.9	8.2

Note: Higher rating (all tests except Digit Symbol) indicates greater performance impairment.

a 0-5 rating from Russell (1975)

b 0-5 rating from Russell, Neuringer, and Goldstein (1970)

c 0-4 rating from Rennick Repeatable Battery

d Age-corrected scaled scores

Marsh J, Brown W, Wolcott D, Carr C, Harper R, Schweitzer S, Nissenson A. rHuEPO treatment improves brain and cognitive function of anemic dialysis patients. Kidney International 1991; 39: 155-163												
Key Questions Addressed	1		2		3		4					
					✓							
Research Question	Change in neurocognitive function for anemic center hemodialysis (CHD) patients											
Study Design	Pre-Post											
Population	**Inclusion Criteria**	Individuals with ESRD currently on CHD; anephric										
	Exclusion Criteria	None reported										
	Study population Characteristics	Variable			Value							
		N			24							
		Age (yrs) mean			46.8±16							
		Mean duration since onset of dialysis			75.7±64 months							
		Mean hematocrit level			23.7±4%							
		Gender M/F			12/12							
		Original diagnosis										
		Chronic glomerulonephritis			7							
		Obstructive uropathy			5							
		Diabetic nephropathy			4							
		Other/Uncertain			8							
	Generalizability to CMV drivers	Unclear										
Methods	Study subjects received HD 3x/wk during study. Dialysis was prescribed to achieve a KT/V (urea) of 1.0 to 1.2 with a PCR of at least 0.8 g/kg/day. Levels were kept constant over the course of the study. Neuropsychological tests performed are discussed in Table G-35. Assessments were undertaken 3 times during the study; before rHuEPO treatment (Pre-T), after 3 months treatment (T+ 3 months); and after 12 months of treatment (T + 12mos). Individuals were scheduled for testing as close to 24 hours post-dialysis as possible.											
Statistical Methods	Repeated measures ANOVA, paired *t*-tests, Pearson correlations											
Quality Assessment	**Internal Validity Category: Low**	1	2	3	4	5	6	7	8	9	10	11
		Yes	NR	NR	NR	Yes	Yes	Yes	NR	No	NR	Yes
Relevant Outcomes Assessed	Neuropsychological function											
Results	Due to scheduling difficulties and refusals to participate, only 19 patients completed first 2 neuropsychological tests while only 14 patients completed all 3 tests. Test results for all 3 study periods are shown in Table G-36. Scores for SDMT improved significantly at three mos. ($t = 2.46$, $p<0.025$) and 12 mos. assessments ($t = 3.22$, $p<0.01$). TMTB scores showed slight improvement at 3 mos. ($t = -0.12$) but significantly improved at 12 mos. ($t = -2.85$, $p<0.025$). Scores for RAVLT and COWAT showed improvement at both 3 and 12 month assessments however scores did not reach significance.											
Authors' Comments	Neuropsychological function improved on all measures after 12 months of rHuEPO treatment of mildly impaired CDH patients.											

Table G-35. Neuropsychological Testing

TEST	DESCRIPTION	SCORING	ASSESSMENT
Trail Making Test Part B (TMTB)	○ Connect circled digits and letters randomly distributed on a page with lines ○ Sequence required is from 1 to A and 2 to B, etc.	Scored in terms of time to complete the task correctly	Attention, visual scanning, psychomotor speed, ability to sequence, and ability to shift cognitive set
Symbol Digit Modalities Test (SDMT)	○ Match printed abstract symbols with a specific digit according to a key which provides the symbol-number match	Number of items correctly completed in a specific time	Learning, memory, psychomotor speed, and scanning efficiency
Controlled Oral Word Association Test (COWAT)	○ Generate as many words as possible starting with the same letter within a specific time period ○ Task repeated 3 times using different letters	Total number of words generated	Verbal fluency, planning and organization, retrieval from semantic memory
Rey Auditory-Verbal Learning Test (RAVLT)	○ Subject learns a list of 15 simple, unrelated words over five trials ○ Second list of 15 words is provided ○ Subject must recall 15 words from original list	Summary score of total number of words recalled on trials 1 to 5	Verbal learning, immediate memory, and retrieval from long-term storage after interference

Table G-36. Neuropsychological Test Scores

Variable	N	Pre-T	N	T + 3 Mos	N	T + 12 Mos	T + 3 mos vs. Pre		T + 12 Mos vs. Pre	
							df	t	df	t
SDMT	17	39.3 ± 11.5	18	45.5 ± 11.4	15	47.0 ± 12.0	16	2.46[a]	13	3.22[b]
RAVLT	18	43.2 ± 14.7	19	49.7 ± 11.3	15	51.0 ± 10.6	17	1.55	13	1.85
COWAT	18	40.5 ± 15.6	19	45.5 ± 13.2	15	49.5 ± 15.3	17	1.60	13	1.64
TMTB	18	114.4 ± 57.5	18	112.6 ± 63.9	15	92.5 ± 51.1	17	−0.12	13	−2.85[a]

Data are presented as means±SD.
[a] $P < 0.025$
[b] $P < 0.01$

Murray A, Tupper D, Knopman D, Gilbertson D, Pederson S, Li S, Smith G, Hochhalter A, Collins A, Kane R. Cognitive impairment in hemodialysis patients is common. Neurology 2006; 67; 216-223														
Key Questions Addressed	1		2		3		4							
	✓				✓									
Research Question	Cognitive performance of hemodialysis patients													
Study Design	Cohort control													
Population	**Inclusion Criteria**	Individuals aged 55+ years on maintenance hemodialysis for at least 2 months at one of 16 clinics in Minneapolis and St. Paul, MN; English as their primary language												
	Exclusion Criteria	Controls were excluded if diagnosed with ESRD or chronic kidney disease (CKD). Individuals were excluded from entire study if previously diagnosed with dementia or International Classification of Disease, Ninth Edition, Clinical Modification equivalents to avoid high population severe cognitive impairments												
	Study population Characteristics	Variable	Hemodialysis patients											
			Primary Cohort	Random Sample	Non-dialysis comparison									
		n	338	101	101									
		Age												
		55-64	29.5	30.7	40.6									
		65-74	31.7	34.7	34.7									
		75-84	30.8	27.7	17.8									
		≥85	8.0	6.9	6.9									
		Mean	71.2±9.5	70.4±9.4	68.5±9.6									
		Gender (female)	45.9	43.6	55.4									
		Dialysis, mo												
		0-12	28.1	32.7										
		13-24	24.0	20.8										
		>24	47.9	46.5										
		Mean duration	32.8±32.8	35.5±42.2										
	Generalizability to CMV drivers	Unclear												
Methods	Dialysis patients were tested once during a 2-day dialysis cycle; 1 hour before dialysis, 1 hour after, or on an "off day". A non-dialysis comparison group of 101 individuals was recruited from outpatient clinics and from the general community. A random sample of 101 hemodialysis patients matched by age was obtained from the 338 individuals in the primary cohort. Participants were administered nine neuropsychological tests over 45 minutes. Testing included Hopkins Verbal Learning Test-Revised (HVLT-R), Color Trails 1 and 2, Stroop Interference Test, Brief Visuospatial Memory Test-Revised (BVMT-R), Controlled Oral Word Association (COWAT), Clock-drawing Test, and Wechsler Digit Span. Using the algorithm shown in Table G-13 cognitive impairment of individuals was divided into the following categories: no, mild, moderate, or severe.													
Statistical Methods	Bivariate analysis; logistic regression													
Quality Assessment	Internal Validity	1	2	3	4	5	6	7	8	9	10	11	12	13
	Category: Low	Yes	No	No	Yes	No	Yes	Yes	No	No	No	Yes	Yes	Yes
Relevant Outcomes Assessed	Cognitive function													
Results	Percentage of the 338 primary cohort who scored ≤1.49 SD, 1.50 – 1.99 SD, and ≥ SD below the age-adjusted norm for cognitive testing is shown in Table G-14. Only 11% scored ≥2.00 SD below the norm on verbal function test (COWAT) however between 35% –													

	40% scored ≥2.00 SD below the norm on tests for memory and executive function domains (Color Trails 2 , 35.8%; BVMT-R, 35.6%; Stroop Interference Test, 41.1%). Frequency of cognitive impairment in the primary hemodialysis patient sample is shown in Table G-15. Results show >70% of the 338 sample group had moderate or severe cognitive impairment (37% severe, 36% moderate); while <30% had mild or normal cognition. Further analysis determined an association among others of duration of dialysis (>24 months) and vascular primary causes of ESRD with severe cognitive impairment (Table G-16). In a comparison of the 101 randomly selected hemodialysis subjects and the nondialysis control group significantly higher cognitive impairment (33.7% vs 11.9%) (Figure G-3) was demonstrated by the HD group. Grouped by age results included severely impaired aged 55-64, 29.0% vs 12.2%; severely impaired aged 65-74, 34.3% vs 5.7%; severely impaired aged 75-84, 32.1% vs 11.1%. In a logistic regression model combining the two groups (n=202), the HD subjects had a high risk of severe cognitive impairment relative to the control group (adjusted OR 3.54; 95% CI, 1.28, 9.78; p <0.02), adjusted for age, gender, ethnicity, education, depression, diabetes, hypertension, and stroke.
Authors' Comments	A high rate of moderate to severe undiagnosed cognitive impairment was found in this HD study population. Investigators recommend initiatives to assess cognitive function for patients prior to beginning dialysis and afterward.

Table G-37. Cognitive Impairment Algorithm

1. Normal: scored ≤1.49 SD below the age-adjusted mean on all tests in all domains*
2. Mild cognitive impairment: scored 1.50 to 1.99 SD below the age-adjusted mean in ≤1 domain
3. Moderate cognitive impairment: scored 1.50 to 1.99 SD below the age-adjusted mean on one or more tests in >1 domain, or ≥2.00 SD below the mean in ≤1 domain
4. Severe cognitive impairment†: scored ≥2.00 SD below the age-adjusted mean on at least one test in ≥2 domains

* The cognitive domains of memory, executive function, and language.
†Classification as severe cognitive impairment requires results of at least one test in each of two or more of the three domains.

Table G-38. Mean Scores (SD) Below Adjusted Means in Primary Hemodialysis Cohort (n=338)

Cognitive test	Raw score, mean (SD)	Percent by number of SDs below adjusted population norms* <1.50	1.50–1.99	≥2.0
3MS (total score)	88.3 (8.6)	59.5	27.5	13.0
Hopkins Verbal Learning (delayed, words)	5.1 (3.2)	48.5	13.3	38.2
Color Trails 2 (time, s)	156.5 (53.9)	57.0	7.2	35.8
BVMT-R (delayed, figures)	4.7 (3.0)	45.8	18.6	35.6
Stroop Interference Test (s)	110.4 (43.3)	49.9	9.0	41.1
COWAT (total words)	26.4 (11.1)	71.3	17.8	10.9
Digit Span	14.7 (3.8)	96.1	3.9†	
Clock-drawing	3.3 (0.8)		26.2‡	
Geriatric Depression Scale	3.2 (2.7)		24.9§	

3MS= Modified Mini-Mental State Examination; BVMT-R= Brief Visuospatial Memory Test Revised;
COWAT= Controlled Oral Word Association Test (given to a subset of 101 of the primary hemodialysis patient cohort).
* Published normative scores were adjusted for age for the Hopkins, BVMT-R, and Stroop; for age and education for Color Trails; and for age, education, and ethnicity for the COWAT.
† 3.9% scored >1.50 SD below normal mean
‡ 26.2% scored ≤ 2 out of 4

Table G-39. Frequency of Cognitive Impairment in Primary Hemodialysis Cohort (n=338)

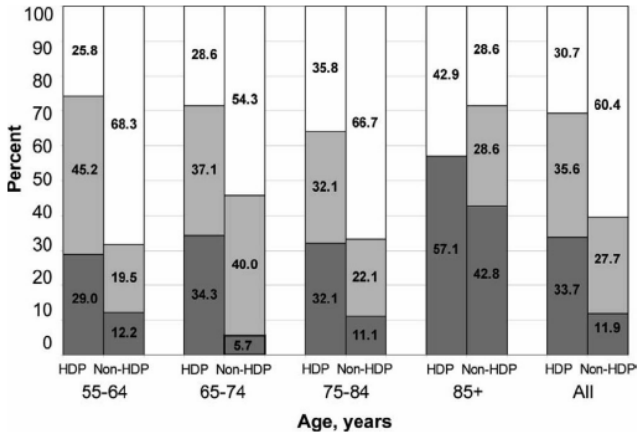
Characteristic	n	Percent with cognitive impairment: None, n = 43	Mild, n = 47	Moderate, n = 122	Severe, n = 126
Age, y					
55–64	100	12.0	10.0	37.0	41.0
65–74	107	14.0	11.2	36.5	38.3
75–84	104	12.5	21.2	34.6	31.7
≥85	27	11.1	11.1	37.0	40.8
Sex					
Female	155	12.3	9.7	40.7	37.4
Male	183	13.1	17.5	32.2	37.2
Education, y					
0–8	38	5.3	7.9	31.5	55.3
9–12	147	9.5	10.2	39.5	40.8
>12	153	17.6	19.0	34.0	29.4
Race					
White	279	15.1	15.8	35.5	33.7
Black	38	0.0	5.3	42.1	52.6
Other	21	4.8	4.8	33.3	57.1
Total	338	12.7	13.9	36.4	37.0

Table G-40. Characteristics Associated with Severe Cognitive Impairment in Primary Hemodialysis Patient Cohort (n=338)

Characteristic	n	Percent with severe cognitive impairment: Yes	No	p*	Adjusted OR (95% CI)	p†
Age, y				0.540		
55–64	100	41.0	59.0		reference	
65–74	107	37.4	62.6		0.77 (0.42, 1.43)	0.410
75–84	104	31.7	68.3		0.57 (0.29, 1.10)	0.090
≥85	27	40.8	59.2		1.05 (0.40, 2.77)	0.910
Sex				0.960		
Female	155	36.7	63.3		0.82 (0.50, 1.35)	0.440
Male	183	37.2	62.8		reference	
Race				0.010		
White	279	33.3	66.7		0.53 (0.24, 1.15)	0.110
Black	38	52.6	47.4		reference	
Other	21	57.1	42.9		1.26 (0.39, 4.10)	0.710
Education, y				0.010		
0–8	38	55.3	44.7		reference	
9–12	147	40.1	59.9		0.42 (0.19, 0.92)	0.030
>12	153	29.4	70.6		0.32 (0.14, 0.72)	0.006
Stroke	70	45.7	54.3	0.100	1.95 (1.08, 3.49)	0.030
Hemoglobin, g/dL‡				0.030		
0.0–10.9	54	50.0	50.0		reference	
≥11.0	282	34.4	65.6		0.56 (0.29, 1.08)	0.080
Months of dialysis				0.050		
0–12	95	28.4	71.6		reference	
13–24	81	33.3	66.7		0.95 (0.47, 1.91)	0.870
>24	162	43.8	56.2		1.65 (0.91, 3.00)	0.100
Primary cause of ESRD						
Vascular				0.030	0.64 (0.33, 1.25)	0.190
Diabetes	131	42.0	58.0			
Hypertension	111	35.1	64.9			
Glomerulonephritis	32	43.8	56.2			
Nonvascular					reference	
PKD	20	20.0	80.0			
Interstitial nephritis	15	20.0	80.0			
Neoplasms, tumors	3	33.3	66.7			
Miscellaneous	26	34.6	65.4			
Equilibrated Kt/V (dialysis dose)‡						
0.0–1.2	148	31.8	68.2	0.070	reference	
>1.2	181	40.9	59.1		1.67 (1.01, 2.75)	0.050

The X^2 test was used for comparisons between categorical variables. Analysis of variance was used for between-group comparisons.
* P For bivariate comparisons between those with and without severe cognitive impairment.
† On logistic regression
‡ Hemoglobin data were missing for two subjects; Kt/V data were missing for nine subjects.
ESRD= end-stage renal disease; PKD=polycystic kidney disease

Figure G-9.Frequency of Cognitive Impairment



Frequency of cognitive impairment in hemodialysis patient (HD) random sample (n=101) and age-matched non-hemodialysis patient sample (n=101). White = normal to mild, light gray = moderate, dark gray = severe cognitive impairment

Murray, A.M., Pederson, S.L., Tupper, D.E., Hochhalter, A.K., Miller, W.A., Li, Q., Collins, A.J., Kane, R., Foley, R.N. Acute Variation in Cognitive Function in Hemodialysis Patients: A Cohort Study with Repeated Measures. Am J Kidney Dis 50: 270-278 (2007)												
Key Questions Addressed	1		2		3		4					
					✓							
Research Question	What is the extent of cognitive functioning among older patients with kidney failure before, during and after hemodialysis treatment?											
Study Design	Pre-post											
Population	Inclusion Criteria	Census of patients 55 yrs and older in 4 outpatient kidney dialysis centers in the Minneapolis-St. Paul MN metropolitan area enrolled in outpatient hemodialysis treatment for at least 3 consecutive months, speaking English as their primary language.										
	Exclusion Criteria	HD persons with medical history of significant psychiatric disorder (psychosis, dementia) including drug and alcohol dependence. HD patient with known noncompliance to treatment. English not primary language.										
	Study population Characteristics	N=30: 12 males, 18 females (66.7%) Mean age: 66.7 y (SD ± 9.5 y) Mean Duration of HD Treatment: 44.7 mos. ± 33.3 mos. Non-white: 12 (42.9 %) Comorbidity: Hypertension (28/40; 93%), Diabetes (28/40; 93%)										
	Generalizability to CMV drivers	Unclear										
Methods	A convenience sample was recruited until a 30 subject total was reached. Three additional HD persons were recruited to compensate for drop-outs. All gave informed consent for study participation. Four (4) testing times were designed to capture cognitive functioning variations: T1 (one hour before HD Therapy); T2 (one hour after commencement of HD treatment); T3 (one hour after HD treatment); and T4 (24 hours after HD treatment). Four examiners were trained in the administration of cognitive test battery and Two HD technicians took physiological measures. A 45 minute-battery of cognitive functioning tests were administered to subjects. Measures included: Mini-Mental State Exam (MMSE): global measure of functioning in population. Controlled Oral Word Association Test (COWAT): timed performance measuring verbal fluency and semantic memory. Hopkins Verbal Learning Test (HVLT): timed performance measuring immediate and delayed verbal memory measuring attention, motor speed, executive functioning and set shifting Brief Visuospatial Memory Test-Revised (BVMT-R): measuring visual memory and spatial relation skills. Geriatric Depression Scale (short version): measures symptoms associated with clinical depression.											
Statistical Methods	Raw scores for cognitive functioning tests were converted to t scores, adjusted for age and education using published norms for each test. A linear model with random effects was used to measure variation in composite *t* scores Model assumptions were tested and found to be normally distributed. A Bonferroni adjustment was employed to control for multiple comparisons of composite *t* scores. Any missing measures were compensated using average scores for the cognitive battery. Practice effects were controlled through random ordering and use of variations in tests Time 1 through Time 4.											
Quality assessment	Study quality= Moderate	1	2	3	4	5	6	7	8	9	10	11
		Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Relevant Outcomes Assessed	HD cohort performance on cognitive tests pre, post and during one dialysis session. Dialysis clearance levels (Kt/V) and serum levels: hemoglobin, hematocrit, creatinine, BUN, phosphorous, calcium, and parathyroid hormone pre, post HD treatment.											
Results	Composite score analyses demonstrated that cognitive functioning among HD patients was significantly lower (poor performance) during HD treatment compared to measures taken one hour prior to treatment ($p < 0.001$). Similarly, cognitive functioning among HD patients during HD treatment was significantly poorer than functioning 24 hours after hemodialysis treatment ($p < 0.001$). Researchers found no significant association between demographic, laboratory and dialysis factors between any two testing intervals.											
Authors' Comments	Data suggests an acute decrease in cognitive functioning during HD treatment. Subjects' neurophysiological patterns are consistent with clinical criteria for delirium and potential long-term functional decline. Given the small sample size, older HD participants and variability in pre-post testing delays for some, generalizability of finding to HD population may be limited.											

Pereira A, Weiner D, Scott T, Chandra P, Bluestein R, Griffith J, Sarnak M. Subcortical cognitive impairment in dialysis patients. Hemodialysis International 2007; 11: 309-314										
Key Questions Addressed	1		2		3		4			
	✓				✓					
Research Question	Level of cognitive impairment of dialysis patients									
Study Design	Historical Cohort									
Population	**Inclusion Criteria**	Patients enrolled from the Dialysis Clinic Inc., Boston hemodialysis unit; aged ≥18 yrs, fluent in English, with MMSE score ≥24; must have been on dialysis for at least 1 month and have Kt/V ≥ 1.2 and hematocrit > 30%.								
	Exclusion Criteria	Individuals with a history of prior stroke, were hospitalized within one month, unable to participate in the neuropsychological survey, or unable to read large font (14 pt. Times New Roman).								
	Study population Characteristics	Variable: n; Age (yrs); Gender M/F — Value: 25; 68.6±12.7; 11/14								
	Generalizability to CMV drivers	Unclear								
Methods	Subject testing included Block Design, Digit Symbol-Coding and Trail Making Tests (A and B).									
Statistical Methods	Chi-square test, *t* test									
Quality Assessment	**Internal Validity Category: Moderate**	1	2	3	4	5	6	7	8	9	10
		No	S	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Relevant Outcomes Assessed	Cognitive impairment									
Results	Cognitive test results are shown in Table G-17. While tests of premorbid intelligence, retention and recognition were similar in comparison to population norms, significant deficits were seen in tests of subcortical or executive function; WAIS-III symbol coding (7.7±3.1 vs 10±3, p=0.001), WAIS-III block design (7.0±1.7 vs 10±3, p<0.001), Trail A (40.5±8.3 vs 50±10, p<0.001) and Trail B (41.8±11.3 vs 50±10, p<0.001).									
Authors' Comments	Mild cognitive impairment was found in this small population of hemodialysis patients.									

Table G-41. Cognitive Test Results

	Function assessed	Consented sample Mean ± SD	Median	Normative data Reference ± SD	p value
MMSE	Cognitive screening	27.5 ± 2.3	28	"Normal" ≥ 24	NA
NAART verbal intelligence quotient	Intelligence	99.5 ± 11.9	100	100 ± 15	0.83
WMS-III Retention	Primarily cortical	11.2 ± 2.6[a]	10	10 ± 3	0.03
WMS-III Recognition		9.1 ± 3.5[a]	9	10 ± 3	0.31
WAIS-III Block design	Primarily subcortical	7.0 ± 1.7[a]	8	10 ± 3	<0.001
WAIS-III Symbol coding		7.7 ± 3.1[a]	7	10 ± 3	0.001
Trail A		40.5 ± 8.3[b,c]	41	50 ± 10[c]	<0.001
Trail B		41.8 ± 11.3[b,c]	43	50 ± 10[c]	<0.001
CESD	Depression	7.8 ± 6.5	6	Depression likely present when CESD > 16	Two subjects (16%) had scores > 16

[a] Normalized for subject age
[b] Normalized for age, gender, and education level
[c] T scores for test performance
CESD = Center for Epidemiological Studies of Depression Scale; age and education associated norms; MMSE= Mini-Mental State Exam; NA = Not applicable; NAART=estimated verbal intelligence quotient from the North American Adult Reading Test; WAIS=Wechsler Adult Intelligence Scale; WMS=Wechsler Memory Scale

Ratner DP, Adams KM,Levin NW, Rourke BP. Effects of hemodialysis on the cognitive and sensorimotor functioning of the adult chronic hemodialysis patient. Journal of Behavioral Medicine 2006; 6:3:291-310.											
Key Questions Addressed	1		2		3		4				
					✓						
Research Question	Assess the effects of hemodialysis on cognitive and sensorimotor functioning										
Study Design	Pre-Post										
Population	**Inclusion Criteria**	Adults diagnosed with ESRD and on maintenance hemodialysis									
	Exclusion Criteria	No patients diagnosed with by medical staff to be acutely ill, diabetic or malnourished, to have a history of known cerebrovascular disease, or to have a predialysis BUN of 50-100mg/100 ml *as determined by each of their last three biweekly predialysis BUN values.*									
	Study population Characteristics	N=20 chronically dialyzed ESRD adults (14 males, 6 females) Mean age: 46.5 years old (SD ± 11.3 years) Mean education level: 13.5 (SD ± 2.0 years) Mean duration on maintenance hemodialysis: 39.7 months (SD ± 21.6 years)									
	Generalizability to CMV drivers	Unclear									
Methods	All patients were on a three times/week dialysis regimen prior to study to assure adequate pre-study dialysis treatment (no change was made is participants characteristic dialysis regimen) and participated in blood sample testing at each study session. Participants received a battery of 14 psychological tests including the Benton Visual Retention, Choice Reaction Time, Color Naming, WAIS Digit Span, WAIS Digit Symbol, Finger Tapping, Grip Strength, Grooved Pegboard, Proverbs, Quick Test, Seashore Rhythm, Speech-Sounds Perception, Trail Making Test, Word Fluency, and Subjective Rating Scale. Each patient received the test battery on 3 consecutive days through a specific schedule. Psychological testing was conducted 2 hours prior to the midweek regularly scheduled weekly dialysis treatment and 20 hours after the midweek treatment. Patients were provided $30 in exchange for completion of research study participation.										
Statistical Methods	Repeated measures one-factor ANOVA										
Quality assessment	Study Quality Category: Moderate	1	2	3	4	5	6	7	8	9	10	11
		Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Relevant Outcomes Assessed	Difference in cognitive and sensorimotor functioning at different times during hemodialysis cycle										
Results	There was little or no evidence to suggest that well-dialyzed patients undergo daily fluctuation in their cognitive and sensorimotor functioning. Mean test scores varied across test administrations from mildly impaired to within normal range. There were significant differences in performance on at least one of the three possible day-pair comparison for 11 of the 27 test measures. Of the 11 cognitive and sensorimotor test measures that were statistically significant on at least one day-pair estimation, six measures showed a significant difference on the D_0(predialysis testing)-D_1(postdialysis testing) day-pair (all improvements in performance)										
Authors' Comments	Despite a daily buildup of toxic renal metabolites, dialysis patients scored within the normal range on the following tests: Chain Reaction Time, Color Naming Time, Digit Span, Finger Tapping (male dominant), Grip Strength (male dominant and nondominant), Proverbs Test, Quick Test, and Seashore Rhythm.										

<table>
<tr><td colspan="12">Umans J, Pliskin NH. Attention and Mental Processing Speed in Hemodialysis Patients. American Journal of Kidney Diseases 1998; Vol 32, No 5: 749-751</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td colspan="3">1</td><td colspan="3">2</td><td colspan="3">3</td><td colspan="2">4</td></tr>
<tr><td colspan="3">✓</td><td colspan="3"></td><td colspan="3">✓</td><td colspan="2"></td></tr>
<tr><td>Research Question</td><td colspan="11">What are the effects of hemodialysis on attention and mental processing?</td></tr>
<tr><td>Study Design</td><td colspan="11">Cohort</td></tr>
<tr><td rowspan="4">Population</td><td colspan="2">Inclusion Criteria</td><td colspan="9">Subjects had to have a fractional urea clearance (Kt/V) greater than 1.0 and hematocrit of 30 or greater for each 6 months prior to study</td></tr>
<tr><td colspan="2">Exclusion Criteria</td><td colspan="9">None reported</td></tr>
<tr><td colspan="2">Study population Characteristics</td><td colspan="9">Measurement — Cases — Controls
Population (n) — 10 — 10
Age (years) — 61±6 — 62±10
Educations (years) — 12.4±3.8 — 11.6±1.0</td></tr>
<tr><td colspan="2">Generalizability to CMV drivers</td><td colspan="9">Unclear</td></tr>
<tr><td>Methods</td><td colspan="11">10 subjects and age and education matched controls participated in study after giving informed consent
All subjects with ESRD had been receiving hemodialysis (HD) 3 times weekly for 0.5 to 10 years without residual renal function
Subjects/Controls did not have history of hospitalization, unstable coronary vascular disease, cerebrovascular disease, depression, uncontrolled hypertension, active collagen vascular disease or vasculitis or use of glucocorticoids or medication with known effects on neuropsychological functioning prior to 6 months
Creatine clearance was estimated in controls b the method of Cockroft and Gault
6 tests were administered including the Stroop Color-Word test, trailmaking test, Digit Span, Paced Auditory Serial Addition test, Continuous Performance test, and the Gordon Diagnostic System Vigilance task
All study participants screened using Beck Depression Inventory to test for evident clinical depression
ESRD subjects tested on a single midweek nondialysis day to reduce the potential effects of varying uremia</td></tr>
<tr><td>Statistical Methods</td><td colspan="11">Data presented in the form of mean ± SD
T-test performed to analyze differences between group means
Criterion corrected for tests because of subtasks included to show significance p<0.05 (two sided) for 6 comparisons</td></tr>
<tr><td rowspan="2">Quality assessment</td><td rowspan="2">Study quality category: Moderate</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr>
<tr><td>No</td><td>S</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="11">Various neuropsychological test batteries performed to test for neurocognitive deficits
Beck Depression test administered to test for clinical depression</td></tr>
<tr><td>Results</td><td colspan="11">Study groups did not differ in age or education years
Groups did not include subjects with unrecognized depression (BDI scores 5.8± 3.3 for ESRD; 4.0±4.3 for controls
Refer to Table G-19 for complete details on testing results</td></tr>
<tr><td>Authors' Comments</td><td colspan="11">"It is unlikely that well-dialyzed patients with ESRD manifest significant uremic neurocognitive deficits in the functional spheres related to sustained attention or mental processing speed."</td></tr>
</table>

Table G-42. Attention and Mental Speed Measures

Test	ESRD	Control
Stroop Word	63.0 ± 12.6	76.1 ± 19.0
Stroop Color	47.8 ± 18.5	57.5 ± 15.7
Stroop Color/Word	23.3 ± 12.2	29.5 ± 12.7
Trails A	68.5 ± 48.1	67.4 ± 57.4
Trails B	313 ± 318	251 ± 252
PASAT 1	24.6 ± 6.9	21.2 ± 10.7
PASAT 2	23.6 ± 5.1	22.9 ± 11.6
PASAT 3	19.5 ± 5.2	21.0 ± 8.9
PASAT 4	17.6 ± 6.6	16.2 ± 8.3
Digit Span	10.6 ± 4.2	12.3 ± 4.1
CPT, no. of hits	308 ± 22	320 ± 6.0
CPT, no. of omissions	15.8 ± 22	3.6 ± 6.0
CPT, no. of commissions	5.3 ± 4.6	6.6 ± 3.4
CPT, RT (msec)	540 ± 74	474 ± 98
GDS, no. of hits	27.6 ± 3.4	26.1 ± 7.3
GDS, no. of omissions	2.4 ± 3.4	3.9 ± 7.3
GDS, no. of commissions	3.4 ± 5.0	1.9 ± 4.9
GDS, RT (msec)	46.9 ± 13.3	47.3 ± 13.1

NOTE. Values expressed as mean ± standard deviation.

Abbreviations: PASAT, Paced Auditory Serial Addition Test; CPT, Continuous Performance Test; GDS, Gordon Diagnostic System Vigilance Task; RT, reaction time.

Williams M, Sklar A, Burright RG, Donovick P. Temporal Effects of Dialysis on Cognitive Functioning in Patients with ESRD. American Journal of Kidney Diseases 2004; Vol 43 No 4: 705-11.				
Key Questions Addressed	**1**	**2**	**3**	**4**
			✓	
Research Question	To examine the temporal fluctuations in memory and attention in subjects with ESRD during the longest interdialytic period of the hemodialysis cycle.			
Study Design	Pre-post			
Population	**Inclusion Criteria**	Subjects with end stage kidney disease (ESRD) age 18 and older Completion of ±3 months of maintenance dialysis therapy before study entry Hemodialysis and CAPD participants were to have stable urea clearance with Kt/V greater than 1.2 and Kt/V greater than 2.0 respectively Hematocrit greater than 30% for ≥3 months		
	Exclusion Criteria	Subjects on the earliest hemodialysis shift of the day History of alcoholism, brain injury, dementia, or psychosis		
	Study population Characteristics	**Measurement** / **Hemodialysis** / **CAPD** Population (n) / 20 / 10 Age (years) / 54.6±2.9 / 45.1±4.8 Women / 10 / 5 Men / 10 / 5 Refer to Table G-43 for complete details		
	Generalizability to CMV drivers	Unclear		
Methods	30 subjects with ESRD from the community hospital dialysis facility volunteered to participate in the study (New York) Subjects on the first shift were not employed or in school All participants received preliminary hearing and vision screens; vision screens included visual acuity and color blindness testing that could impair neuropsychological performances Several neuropsychological tests administered including Dodrill Stroop that tests selective attention, Rey Auditory-Verbal learning test used to evaluate memory functioning; intelligence measures administered including the Kaufman Brief Intelligence test—a psychometric test providing measures of verbal and non-verbal intelligence Beck Depression Inventory II tests administered to assess symptoms of depression and the effects on cognitive performance Repeated measures for stroop and RAVLT administered to 20 hemodialysis subjects examining the fluctuations of cognitive performance since dialysis; test repeated for the 10 CAPD subjects for comparisons Hemodialysis subjects given 1 hour after the Friday or Saturday hemodialysis session (T1); (T2) is 24 hours after T1 and T3 is 67 hours after T1 "Baseline for T1 for CAPD subjects established arbitrarily" Subjects asked to record levels of fatigue at each time stamp to test for the potential impact of fatigue post-dialysis Likert scale used to measure subjectively; range 1, no fatigue to 5 overwhelming fatigue (sleeping)			
Statistical Methods	Data analyzed using SPSS 10.0 for Windows (statistical software, SPSS Inc, Chicago, IL) Descriptive data, 2 factor mixed analysis of variance (ANOVA) used Chi-square analysis, paired-sample t-tests, ans well as independent-sample-t-tests Psychological measures included All data expressed as mean ± SE; p of 0.05 used as statistical significance			

Quality assessment	Study quality category: Moderate	1	2	3	4	5	6	7	8	9	10
		Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Relevant Outcomes Assessed	Likert scale used to measure fatigue subjectively Psychological measures performed to test for cognitive abilities/inabilities
Results	Comparison of older subjects ≥50 with younger ≤49 hemodialysis and CAPD groups did not differ significantly in age distributions

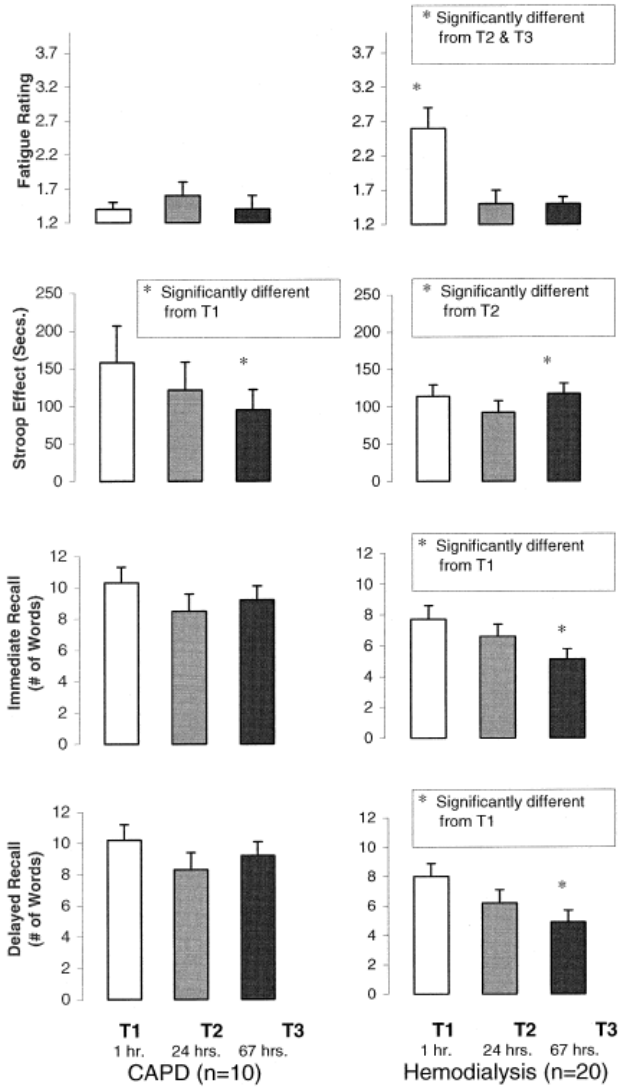
	Chi-square showed no differences in level of education and income Average of dialysis therapy 30 months longer in hemodialysis group compared to CAPD subjects independent-samples *t*-test analysis indicated the groups did not differ significantly in dialysis vintage Hemodialysis group showed a decline in performance at T3 compared to T2 (t=-2.65; df=19; p<0.05) CAPD group improved performance for T2 and T3 compared to T1 (t=2.32; df=9; p< 0.05 and t=2.65; df=9; p<0.05, respectively) Hemodialysis group had less word recall at T3 during RAVLT (t=-3.36; df=29; p<0.005) compared to CAPD group Hemodialysis group had significantly fewer words than CPAD group (t=-3.58; df=29; p<0.005) Refer to Figure G-10 for complete details
Authors' Comments	"Our data suggest that fatigue does not account for the deterioration in mental acuity in these patients. Rather, the fluctuation of psychometric measures in temporal correlation with hemodialysis treatments suggests that increasing accumulation of toxic uremic metabolites in the interdialytic period is involved in cognitive fluctuations. It should be noted that although vintage time between the hemodialysis and CAPD group was not statistically significant, the 30-month increase in vintage time for the hemodialysis group could have clinical significance."

Table G-43. Characteristics of Study Participants

Age (y)	54.6 ± 2.9	45.1 ± 4.8
Women	10	5
Men	10	5
Education		
≤Grade 12	1	2
High school diploma/GED	10	3
Some college	8	4
College degree	1	1
Ethnicity		
Caucasian	18	8
African American	2	1
Other	0	1
Income ($)		
<10,000	6	4
10,001-19,999	7	4
20,000-39,999	3	2
>40,000	4	0
Duration of dialysis (mo)	65.4 ± 13.1	36.1 ± 7.2
Cause of ESRD		
Diabetes	6	5
Hypertension	4	2
Glomerulonephritis	3	0
Polycystic kidney disease	2	1
Other	5	2
Mean IQ (K-BIT)	104.8 ± 1.8	102.2 ± 4.0
Mean depression symptoms (BDI-II)	11.9 ± 1.8	17.4 ± 3.0

NOTE. Values expressed as mean ± SE or number of patients, unless noted otherwise.

Figure G-10. **Mean ±SE for fatigue scores, Stroop Effect, and total words generated in the immediate and delayed recall of the RAVLT for the hemodialysis and CAPD groups at 1, 24, and 67 hours after hemodialysis and after baseline for the CAPD group.**



Key Question 3: Sleep-related Evidence

<table>
<tr><td colspan="12">Hanley, P.J., Pierratos, A. Improvement of Sleep Apnea in Patients with Chronic Renal Failure Who Undergo Nocturnal Hemodialysis. N Engl J Med 344: 102-7 (2001).</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td></tr>
<tr><td></td><td></td><td>✓</td><td></td></tr>
<tr><td>Research Question</td><td colspan="11">Does nocturnal dialysis improve symptoms of sleep apnea associated with chronic kidney failure among patients who had previously undergone traditional hemodialysis treatment?</td></tr>
<tr><td>Study Design</td><td colspan="11">Pre-and Post Measures</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="10">Census of patients of university-based medical center diagnosed with chronic renal failure enrolled in outpatient hemodialysis therapy.
Candidates for home-centered nocturnal dialysis therapy (1993-1998).</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="10">Non-English-speaking
Inability to respond to telephone prompts and remote monitoring.
Absence of central venous access for dialysis mechanism.
Unskilled in self-operation of dialysis mechanisms.
Unsupportive home environment.
Contraindications for anticoagulation treatment.</td></tr>
<tr><td>Study population Characteristics</td><td colspan="10">N=14 (10 males, 4 females)
Mean age: 45 years (SD ± 9 y)
Duration of Hemodialysis Treatment : 1 – 15 y</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="10">Unclear</td></tr>
<tr><td>Methods</td><td colspan="11">14/15 (93%) of eligible home-centered nocturnal dialysis candidates agreed to participate in study with informed consent.
Before transition to nocturnal hemodialysis, participants underwent polysomnography in a lab setting.
Between 6 to 15 months after transition from outpatient hemodialysis treatment (up to 4 hrs. 3x per week) to nocturnal dialysis (6-8 hrs. 6 days/wk) and patient status was normalized, recruited patients agreed to travel to sleep lab for measures on two occasions 1) sleep with dialysis and 2) sleep w/o dialysis – random assignment.
Baseline (pre-nocturnal dialysis) serum and polysomnagraphy measures were recorded and averaged for comparison purposes where appropriate.
None of the participants had been assessed for sleep apnea prior to intake. One patient had been diagnosed with Cheyne-Stoakes Respiration (Nasal) Disorder.</td></tr>
<tr><td>Statistical Methods</td><td colspan="11">Pre-post measures group mean values were analyzed using Student's t-tests.
Analysis of variance for repeated measures employed the Bonferroni test.
A two-tailed $p < 0.05$ was selected for the upper-limit for significance testing.</td></tr>
<tr><td rowspan="2">Study Quality Assessment</td><td rowspan="2">Pre-Post Study Quality = Moderate</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td></tr>
<tr><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="11">Apnea-Hypopnea Index post- treatment normalization.
Serum creatinine concentrations post-treatment normalization.</td></tr>
<tr><td>Results</td><td colspan="11">The conversion from conventional hemodialysis to nocturnal dialysis was positively associated with a reduction in the number of apnea-hypopnea sleep events among all cohort members ($p < 0.03$).
This positive reduction was demonstrated in 7/15 patients who met criteria for diagnosis of sleep apnea (46 events ± 19 to 9 ± 9; $p < 0.006$).
Significant improvements in nocturnal vs. conventional hemodialysis were also seen in lower averaged serum creatinine levels ($p < 0.001$).</td></tr>
<tr><td>Authors' Comments</td><td colspan="11">"CAPD patients showed cognitive stability, whereas hemodialysis patients showed temporal fluctuations in cognitive performance."</td></tr>
</table>

Jean G, Piperno D, Francois B, Charra B. Sleep apnea incidence in maintenance hemodialysis patients: influence of dialysate buffer. Nephron 1995; 71: 138-142					
Key Questions Addressed	1	2	3	4	
			✓		
Research Question	Influence of acetate or bicarbonate hemodialysis buffer on sleep function for dialysis patients				
Study Design	RCT				
Population	**Inclusion Criteria**	None reported. Enrolled individuals were men and women aged 35-71 with ESRD treated with hemodialysis			
	Exclusion Criteria	Individuals with hypothyroidism, abused alcohol, obese, used hypnotics, and with obvious airway narrowing			
	Study population Characteristics	Variable: Value N: 10 Gender M/F: 8/2 Age (yrs): range 35 – 71 Weight: 55 – 72 kg Duration of hemodialysis: 6 – 67 months Predialytic systolic blood pressure (mean): 139±9 mm Hg Additional patient characteristics noted in Table G-44.			
	Generalizability to CMV drivers	Unclear			
Methods	Pts received a standard dialysis of 5 hours, 3x/wk using acetate dialysis or bicarbonate dialysate and AN69 polyacrylonitrile dialyzers. Pts responded to a sleep habit questionnaire; five subjects complaining of SAS-related symptoms including daytime sleepiness, disturbed nocturnal sleep, morning headaches, restlessness and snoring during sleep. Assessments were conducted on a night following a mid-week hemodialysis (HD) session (2:00 pm - 7:00 pm) Pts spent 2 nights in the sleep lab from 9:00 pm – 7:00 am; once following a series of six sessions with acetate or bicarbonate and once after a series with the other buffer. Sequence of buffers was randomly assigned between 10 pts Disorders of breathing events (DBEs) are apneas and hypopneas. Sleep apnea is defined as the occurrence of at least 5 DBEs/hr or at least 30 DBEs/night				
Statistical Methods	Non-parametric Wilcoxon paired test				
Quality assessment	Study quality category: Low	1: Yes 2: NR 3: Yes 4: Yes 5: NR 6: NR 7: Yes 8: Yes 9: Yes 10: Yes 11: Yes 12: Yes 13: NR 14: NR 15: NR 16: NR 17: NR 18: Yes 19: Yes 20: Yes 21: Yes 22: Yes 23: Yes 24: NR 25: Yes			
Relevant Outcomes Assessed	Number of disordered breathing events (DBEs)				
Results	Results for sleep-related respiration included 6/10 pts (60%) with pathologic DBEs during the acetate hemodialysis (AH) night and 5/10 (50%) during the bicarbonate hemodialysis (BH) night (Table G-45). A decrease was demonstrated in the total number of DBEs during the BH night for all pts but particularly evident for central apnea (33 versus 3, mean; p=0.04) and episodes of hypopnea (114 versus 64; p = 0.05). Although apnea episodes were short in all patients, a trend towards a longer mean total duration of DBEs was demonstrated during the AH night (23 vs 13 min). Sleep disordered symptoms were not significantly correlated to sleep apnea episodes.				
Authors' Comments	"Gender, age, weight, date of first dialysis, blood pressure and sleep disorder-related symptoms were not correlated with the sleep apnea syndrome…. A defective modulation of ventilatory control after acetate HD might be held responsible for central apnea, which would constitute one more case for a widespread use of bicarbonate HD."				

Table G-44. Patient Data

No.	Sex	Age years	Weight kg	Dialysis months	HBP	SAS-related symptoms	SAS on study
1	m	70	72	27	–	+	+
2	m	70	66	37	–	+	–
3	m	55	63	25	–	+	++
4	m	48	70	7	+	–	+/–
5	f	48	49	11	+	–	++
6	m	63	59	67	–	–	+
7	f	34	41	7	+	–	–
8	m	40	54	6	+	–	–
9	m	40	65	7	+	+	++
10	m	65	62	66	–	+	–

Patient data before the study and their relations with pathologic apneas on the polysomnographic recordings.
HBP: high blood pressure

Table G-45. PSG Results

	Acetate	Bicarbonate	p (Wilcoxon)
Patients with SAS	6/10	5/10	
Sleeping time, min	359 (311–400)	300 (210–380)	0.04
Apnea/night	90 (11–337)	45 (5–150)	0.03
Obstructive	36 (11–93)	35 (5–120)	NS
Central	33 (0–188)	3 (0–15)	0.04
Mixed	6 (0–31)	4.1 (0–21)	NS
Apnea time, min	23 (2–87)	13 (1–50)	NS
Hypopnea/night	114 (25–195)	64 (12–176)	0.05
Hypopnea time, min	36 (5–70)	17.8 (2–77)	NS
Mean SaO_2, %	96.3 (95–98)	96 (94–97.6)	NS
Time >95% SaO_2, %	87.5 (67–99)	77 (41–100)	NS
Time <90% SaO_2, %	0.7 (3–0)	0	NS

Values represent means with the range given in parentheses.

Unruh M, Sanders M, Redline S, Piraino B, Umans J, Hammond T, Sharief I, Punjabi N, Newman A. Sleep apnea in patients on conventional thrice-weekly hemodialysis: comparison with matched controls from the Sleep Heart Health Study. J Am Soc Nephrol 2006; 17: 3503-09											
Key Questions Addressed	1		2		3		4				
	✓				✓						
Research Question	Association of sleep disordered breathing (SDB) and hemodialysis (HD)										
Study Design	Cohort										
Population	**Inclusion Criteria**	Individuals undergoing in-center HD 3x/wk at one of 24 centers in Western PA; participated in studies performed from May 2004- September 2005. Controls had participated in the ongoing Sleep Heart Health Study (SHHS) from 2001-2002									
	Exclusion Criteria	Individuals with craniofacial abnormalities, age <45 yr or >90 yr, active malignancy, active infection (pneumonia), active coronary artery disease (i.e., MI, unstable angina) within the last 6 months, advanced cirrhosis, advanced dementia, or active alcohol abuse and those with refractory psychiatric disease; patients using continuous positive airway pressure, oral devices, or home oxygen therapy; pts with tracheostomy									
	Study population Characteristics		Case	Control							
		n	46	137							
		Age (yr)	62.7±10.1	62.7±10.1							
		Gender Male	33 (71.7%)	98 (71.5%)							
		BMI (kg/m^2)	28.0±5.4	28.1±5.3							
		Lung disease	5 (10.8%)	23 (16.7%)							
		CVD	15 (32.6%)	17 (12.5%)							
		Diabetes	15 (32.6%)	12 (8.8%)							
		HD Treatment (median)	22 month (9-46 mo)								
	Generalizability to CMV drivers	Unclear									
Methods	All participants underwent polysomnography (PSG) overnight between 8:00 pm and 8:00 am. Medical history, sleep habits and subjective sleepiness information was obtained by interview, questionnaire and Epworth Sleepiness Scale, respectively.										
Statistical Methods	Log-log transformation, conditional logistic regression, mixed-effects regression model, conditional logistic regression techniques										
Quality Assessment	**Study quality category: Moderate**	1	2	3	4	5	6	7	8	9	10
		No	S	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Relevant Outcomes Assessed	Rate of sleep disordered breathing										
Results	Differences between groups include a higher rate of alcohol use in the SHHS sample, a higher systolic BP and a higher proportion of diabetes and CD in the HD group (Table G-20). An average mean single-pool Kt/V>1.2 or urea reduction rate >0.66 demonstrated adequate dosages of dialysis were being received. Results for sleep parameters are shown in Table G-21. Sleep time for the HD group was significantly shorter than the SHHS group (319.5±106.3 vs 378.9±67.3). Similar sleep efficiency was demonstrated (78.1±15.3 vs 81.3±10.4); and similar Stage 1 (5.0±3.4 vs 5.5±3.65) and Stage 2 sleep (57.6±14.3 vs 58.4±11.5). HD patients had significantly more Stage 3 to 4 sleep (23.4±12.2 vs 14.3±10.7, p<0.001); less REM sleep (13.6±8.2 vs 21.7±6.2, p<0.001); higher arousal index (25.1±14.6 vs 17.1±8.0); higher RDI (27.2±19.3, 15.2±4.9, p<0.001); and higher hypoxemic index (7.2±20.8 vs 1.84±8.4, p<0.001). Similar responses were shown for subjective sleepiness reported by ESS (9.0±4.7 vs 8.0±4.3). The HD sample had significantly higher odds of severe SDB (RDI>30; crude: odds ratio [OR] 3.49 [95% CI 1.5 to 7.9]; adjusted for history of diabetes and CVD: OR 4.02 [1.5 to 10.2].										
Authors' Comments	HD patients had four-fold higher odds of having severe SDB. Generalizability of these results is supported by study recruitment from several HD units, adequate HD dosage and inclusion of a racially diverse sample.										

Study Summary Tables for Key Question 4

Key Question 4: Neurocognitive Evidence

Griva K, Thompson D, Jayasena D, Davenport A, Harrison M, Newman SP. Cognitive functioning pre- to post-kidney transplantation-a prospective study. Nephrol Dial Transplant 21: 3275-3282 (2006).

Key Questions Addressed	1	2	3	4	
				✓	
Research Question	Prospectively evaluate and compare the neuropsychological (NP) functioning pre- to post-kidney TX using a larger number of NP Tests to cover a range of cognitive domains; and to identify the predictors of NP changes pre- to post TX				
Study Design	Pre-post, Historical control				
Population	**Inclusion Criteria**	Individuals who are: (1) at least 18 years of age or greater, (2) no history or clinically evident cerebrovascular disease as reflected by new, transient or fixed neurological deficits, (3) no major visual or hearing impairments, or other sensory or motor impairments that prohibit them from completing the scheduled assessments, (4)absence of acute or chronic psychosis, evident depression, severe learning disabilities and/or dementia, (5) currently stable, defined as not being acutely ill or hospitalized at the time of the assessments, (6) be fluent in written and spoken English (7) a minimum of 3 months on their respective mode of treatment and dialysis techniques and (8) diagnosed with ESRD.			
	Exclusion Criteria	None reported			
	Study population Characteristics	N=28 medically stable patients (16 males, 12 females) Mean age: 44.04 years old (SD ± 12.01 years) Average Time on Dialysis: 30.96 months (SD ± 32.81) Dialysis Treatment: Hemodialysis – 10 months (SD ± 35.7); Peritoneal dialysis – 18 months (SD ± 64.3) Average Time from baseline to Transplant (TX): 14.88 months (SD±8.56)			
	Generalizability to CMV drivers	Unclear			
Methods	28 medically stable patients with ESRD were selected from a patient population of 146 dialysis patients. The participants were investigated before and at 6 months after successful kidney TX. An NP test battery (Trailmaking Tests A and B, Symbol Digit Modalities Test, Rey Auditory Verbal Learning Test, Benton Visual retention Test and Grooved Pegboard) was used and assessed attention-concentration, psychomotor ability and memory. During dialysis and 6 months post-kidney TX, the test battery and study questionnaire were administered to participants. During dialysis time period, patients were assessed twice within a 24 hour time interval to ascertain acute NP changes from pre- to post-dialysis. At the 24 hour time period (post dialysis), the second assessment NP scores were used as baseline measures for comparison with performance post-transplantation. In judging patient performance on NP tests relative to normative performance, individuals' performances on each of the NP tests were compared with a normative sample. An individual's NP performance was considered impaired on a particular test if it was >1 SD below the mean of the norms. This comparison was performed for all the NP tests except the Benton visual Retention Test (BVRT) scores where clinical cut-offs (indicative of NP impairments) were used. Based upon BVRT score clinical cut-offs (classified as 'impaired' or 'not impaired'), the frequency of NP impairments pre- to post-TX was computed.				
Statistical Methods	Repeated measures ANOVA Pearson correlations				

Quality assessment	Pre-post Study Quality: Moderate	1	2	3	4	5	6	7	8	9	10	11
		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Quality assessment	Historical Cohort Study Quality: Low	1	2	3	4	5	6	7	8	9	10	
		No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	

Relevant Outcomes Assessed	Improvement in cognitive functioning post-kidney TX., comparison of transplant recipients to normative data

Results	A series of repeated measures ANCOVAs were performed to compare NP performance. Pre- to post-TX test scores are reported in **Error! Not a valid bookmark self-reference.**. Patients performance in verbal and non-verbal memory tasks improved significantly after TX compared with the dialysis NP scores (RAVLT-T [*F*(3, 25) = 19.79, P=0.0002], BVRT-C [*F*(3,25) = 9.07, *P*=0.006]. Normative comparisons also indicated an improvement in memory following TX. While 11 patients (39%) performed worse than their age-respective norms on the verbal memory task at dialysis (more than double than expected in a normal distribution), only 4 pts (14%) performed worse than their age norms at the post-TX evaluations. BVRT-E and SDMT-W showed a trend for improvement however these did not reach significance. In a comparison of NP performance relative to norms, performances indicated that cognitive functioning was not impaired as a whole (performances were all within 1 SD of the population mean). In further investigation of individual differences in performance indicated NP impairments (as indexed by individual scores >1 SD lower than the expected age norms) were evident for a considerable number of patients, specifically at baseline/dialysis assessment. After six months post-TX however, the likelihood of NP impairments decreased substantially (Table G-47). The proportion of scores post-TX 1 SD below the mean is similar to that which would be expected in a normal distribution (15.86%).
Authors' Comments	Study participants showed significant improvement in cognitive functioning 6 months post-TX. A significant improvement was demonstrated post-TX for both verbal and non-verbal memory tasks (RAVLT-T and BVRT-C).

Table G-46. Mean and SD of absolute NP scores pre- to post-TX

	T1: dialysis		T2: TX		*F*	*P-value*
	M (SD)	Range	M (SD)	Range		
TMT-A[a]	37.83 (19.05)	83.62	32.49 (17.48)	68.75	0.003	0.960
TMT-B[a]	77.45 (35.12)	127.28	77.20 (41.81)	182.92	0.238	0.630
SDMT-W[b]	49.43 (14.45)	49	53.29 (13.71)	51	3.849	0.061
SDMT-O[b]	52.68 (14.34)	50	59.18 (15.18)	56	2.096	0.160
RAVLT-T[b]	43.14 (10.04)	32	53.21 (9.16)	38	19.792	0.000
GP-D[a]	78.63 (21.61)	99.59	75.28 (22.56)	103.7	0.941	0.342
GP-ND[a]	86.31 (27.73)	120	86.57 (27.88)	112.13	0.000	0.995
BVRT-C[b]	5.82 (2.33)	9	7.14 (2.01)	6	9.069	0.006
BVRT-E[c]	6.64 (4.80)	17	4.08 (3.32)	10	4.193	0.051

T1, time 1, baseline assessment; T2, time 2, post-TX assessment; TMT-A, Trail Making Test, part A; TMT-B, Trail Making Test, part B; SDMT-W, Symbol Digit Modality Test, written administration; SDMT-O, Symbol Digit Modality Test, oral administration; RAVLT-T, Rey Auditory Verbal Learning Test, total word recall at trial 1–5; GP-D, Grooved Pegboard, dominant hand; GP-ND, Grooved Pegboard, non-dominant hand; BVRT-C, Benton Visual Retention Test, number of correct reproductions; BVRT-E, Benton Visual Retention Test, number of reproduction errors.
[a]Time to completion (in seconds).
[b]Number correct.
[c]Number of errors.

Table G-47. Prevalence of NP impairments pre- to post-TX

	Time 1 Dialysis *N impairment (%)*	Time 2 Transplantation *N impairment (%)*	*P-value**
TMT-A[a]	5 (17.9)	5 (17.9)	1.00
TMT-B[a]	4 (14.3)	4 (14.3)	1.00
SDMT-W[a]	7 (25)	5 (17.9)	0.317
SDMT-O[a]	8 (28.6)	5 (17.9)	0.083
RAVLT-T[a]	11 (39.3)	4 (14.3)	0.035
GP-D[a]	5 (17.9)	5 (18.5)	1.00
GP-NDOM	7 (25)	6 (22.2)	0.655
BVRT-C[b]	5 (17.9)	1 (3.6)	0.034
BVRT-E[c]	7 (25)	3 (10.7)	0.046

T1, time 1, baseline assessment; T2, time 2, post-TX assessment; TMT-A, Trail Making Test, part A; TMT-B, Trail Making Test, part B; SDMT-W, Symbol Digit Modality Test, written administration; SDMT-O, Symbol Digit Modality Test, oral administration; RAVLT-T, Rey Auditory Verbal Learning Test, total word recall at trial 1–5; GP-D, Grooved Pegboard, dominant hand; GP-ND, Grooved Pegboard, non-dominant hand; BVRT-C, Benton Visual Retention Test, number of correct reproductions; BVRT-E, Benton Visual Retention Test, number of reproduction errors.

*McNemar tests

[a] More than 1 SD below normative mean

[b] Four or more lower than the expected scores for number correct.

[c] Five or more errors than expected norms.

<table>
<tr><td colspan="5">Kramer, L., Madl, C., Stockenhuber, F., Yeganehfar, W., Eisenhuber, E., Derfler, K., Lenz, K., Schneider, B., Grimm, G. Beneficial Effect of Kidney transplantation on Cognitive Brain Function. Kidney International; 49: 833-838. (1996).</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td></tr>
<tr><td>✓</td><td></td><td></td><td>✓</td></tr>
<tr><td>Research Question</td><td colspan="4">Does kidney transplantation improve cognitive functioning among persons with ESRD enrolled in hemodialysis?</td></tr>
<tr><td>Study Design</td><td colspan="4">Cohort controlled; Pre-Post Measures of Cases</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="3">Cases: Outpatients associated with the Departments of Medicine III and IV, University of Vienna, Austria enrolled in hemodialysis treatment due to ESRD and candidates for either cadaveric or living-donor kidney transplantation.
Controls: Volunteers associated with the University of Vienna with no evidenced kidney disease.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="3">Persons who were psychiatrically impaired, as scored by screening exam, those evidenced having neurological, vascular or immunological complications. Persons with systemic diseases such diabetes, malignant hypertension and multiple myeloma were also excluded.</td></tr>
<tr><td>Study population Characteristics</td><td colspan="3">
<table>
<tr><td>Measure</td><td>Case</td><td>Control</td></tr>
<tr><td>Population (n)</td><td>15</td><td>45</td></tr>
<tr><td>Age y</td><td></td><td></td></tr>
<tr><td>(mean ± SD)</td><td>45 ± 13</td><td>NR</td></tr>
<tr><td>Male %</td><td>7 (47%)</td><td>NR</td></tr>
<tr><td>Duration of Dialysis</td><td></td><td></td></tr>
<tr><td>Median mos.</td><td>16</td><td>NA</td></tr>
<tr><td>Range mos.</td><td>3 – 96</td><td>NA</td></tr>
<tr><td>Comorbid Condition:</td><td>8/15 (53%)</td><td>NA</td></tr>
</table>
</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="3">Unclear</td></tr>
<tr><td>Methods</td><td colspan="4">With the approval of the Internal Review Board, informed consent was given by participants for study inclusion.
Out of a total pool of 169 available volunteers, 45 were chosen for gender and age-match to ESRD/Trans participants (data not shown). Controls submitted to blood sampling.
ESDR/Trans participants were tested no more than 24 hours after a routine hemodialysis session, establishing baseline measures for cognitive functioning as described below and recent serum analyses.
Measures of Cognitive Functioning:
Evoked Potential Measures (EPM): electrical impulses as recorded through electrodes places on face and skull. Pip tones were binaurally channeled through earphone connection.EEG epogues were of 800 ms were electronically recorded after each tone and electronically recorded. Troughs and peaks were calculated to P300 (latency) and N400 (amplitude) and according to standard methods for the electrodiagnostic system.
Trailmaking Test: Tucson: Neuropsychology Test, 1982. Short-term memory and sensorimotor reaction time.
Mini-mental State: screening for neuropathology, severe psychiatric illness for clinicians, 1975.
Serum Measures:
Hemoglobin g/dl
Hematocrit %
Creatinine mg/dl
BUN mg/dl
To evaluate the effect of hemoglobin levels on cognitive functions, 6 patients from the same case census (in hemodialysis) were chosen for data comparison. These patients had normal hemoglobin levels. Six patients (in hemodialysis) with severe anemia were also selected. Patient participants were given same battery of tests.
ESDR/Trans participants were again given the battery of tests and serum measures about a year after kidney transplantation (14 ± 5 mos.).
Researchers note that will transplantation-related chemotherapy to reduce complications and graft rejection commenced at time of surgery. The regimen included cyclophosphamide (n=10), prednisolone (n=10) and five (5) patients received azathioprine. All received recombinant erythropoietin therapy. One patient received therapy to control for HLA-antibodies.</td></tr>
</table>

<table>
<tr><td>Statistical Methods</td><td colspan="12">Results obtained at baseline and after transplantation were compared using Student's t-test or Wilcoxin test for paired data.
Tests of data normality were performed using the Wilk-Shapiro method.
Comparison of within and between groups was performed with either ANOVA or the Wilcoxon test for paired data.
Associations of all research variables were investigated using the Pearson or Spearman correlations coefficients.</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Study quality Category: Cohort Moderate</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr>
<tr><td>No</td><td>S</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td></tr>
<tr><td rowspan="2">Study quality Category: Pre-post Moderate</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td></tr>
<tr><td>Yes</td><td>NR</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="12">Pre- and post-transplantation serum and cognitive function measures within and between case and control group comparison.</td></tr>
<tr><td>Results</td><td colspan="12">Before transplantation, researchers demonstrated a significant correlation among and between these measures: P300 latency (EPM) which detected poor cognitive functioning among ESDR/Trans group in with age, hemoglobin, hematocrit, BUN levels compared to matched group ($p < 0.01$).
No significant correlation between electrophysiological data and blood assay measures was detected.
Post-transplantation, age was the only parameter correlated to P300 (poor cognitive function) among the case group. This same correlation was found in the control subjects ($p < 0.05$)
Following kidney transplantation (approx. 14 mos. Post-graft) EPM (2 central indices of cognitive functioning) scores described above significantly improved compared to baseline scores ($p < 0.01$; $p < p\ 0.05$).
Post-transplantation patients (14 mos.) showed no significant differences in EPM, Trailmaking Tests and Mini-Mental State Tests compared with matched control group.</td></tr>
<tr><td>Authors' Comments</td><td colspan="12">Researchers conclude that cognitive dysfunction among HD patients , with successful kidney transplantation may be fully reversed. These reversals and improvements in cognitive functioning, with transplantation, are evident in those patients who have been in HD treatment for long periods of time..</td></tr>
</table>

Key Question 4: Sleep-related Evidence

Molnar M, Szentkiralyi A, Lindner A, Czira M, Szabo A, Mucsi I, Novak M. High prevalence of patients with a high risk for obstructive sleep apnoea syndrome after kidney transplantation-association with declining renal function. Nephrol Dial Transplant 2007; 22: 2686-2692

Key Questions Addressed	1		2		3		4				
							✓				
Research Question	Association of declining renal function with increased prevalence of high risk for obstructive sleep apnea syndrome										
Study Design	Cohort										
Population	**Inclusion Criteria**	All pts aged >18 yrs who regularly presented at a single outpatient transplant center at the Dept of Transplantation and Surgery at the Semmelweis University, Budapest; received their transplant between 1977-2002. Individuals waitlisted and receiving dialysis in Budapest									
	Exclusion Criteria	None reported									
	Study population Characteristics	Variable	Transplant (TX)	Waitlisted (WL)							
		N	841	175							
		Gender M/F (%)	59/41	61/39							
		Age (yrs) (mean±SD)	49±13	48±13							
		BMI (mean±SD)(kg/m^2)	25±4	26±5							
		Diabetes (%)	17	18							
		Number of comorbid conditions (median; min-max)	2 (0-7)	2 (0-6)							
		Cumulative ESRD time (median; IQR) months	79; 71	36; 43							
	Generalizability to CMV drivers	Unclear									
Methods	Patient information obtained included demographics and medical history. Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Kidney disease (MDRD) study formula: eGFR(ml/min./1.73m^2)=186 x $^{-1.154}$(Age)$^{-0.203}$ (x 0.742 if female). Based on the eGFR, pts were classified into groups corresponding to CKD stages suggested by the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines: group 1: eGFR≥60ml/min./ 1.73m^2 (≥1 ml/sec./ 1.73m^2); group 2: eGFR 30-59 ml/min./ 1.73m^2 (0.5-1 ml/sec./ 1.73m^2); group 3: eGFR 15-29 ml/min./ 1.73m^2 (0.25-1 ml/sec./ 1.73m^2); group 4: eGFR <15 ml/min./ 1.73m^2 (<0.25ml/sec./ 1.73m^2). Berlin sleep apnea questionnaire assessed risk of OSA with a series of 10 questions grouped into 3 domains (snoring behavior/presence of apnea, consequences of the apnea, and hypertension/abnormally high BMI) Pts were classified as "high risk" when positive for ≥2 domains; and "low risk" if ≥2 domains are negative. Presence or absence of comorbidity was self-reported. A comorbidity score was calculated for total number of comorbid conditions reported.										
Statistical Methods	Student's *t* test, Mann-Whitney *U* test, logistic regression										
Quality assessment	Study quality category: Moderate	1	2	3	4	5	6	7	8	9	10
		No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Relevant Outcomes Assessed	Risk of obstructive sleep apnea										
Results	Distribution of underlying kidney diseases was similar in the TX and WL groups with the exception of proportion of chronic pyelonephritis/tubulointerstitial nephritis being significantly smaller (11% vs 22%; p<0.001) and unknown kidney disease was significantly higher (28% vs 13%; p<0.001) in TX vs WL group, respectively.										

	9% of pts had more than one kidney TX. 88% of TX group correctly responded to the Berlin Sleep Apnea Questionnaire. A similar prevalence of high risk for OSA was found for both groups; 27% of TX group (n=231) vs 33% of WL group (n=58)(p=0.079)(Table G-48). Kidney transplanted pts with a high risk of sleep apnea were significantly older (52±11 years vs 47±13 years, p<0.001)(Table G-49) and had significantly higher BMI (27±5 kg/m^2 vs 24±4 kg/m^2; p<0.001) than pts without sleep apnea. Proportion of males in the "high risk" group was significantly higher than in the "low risk" group (64% vs 56%, p<0.05)(Table G-49). The number of self-reported comorbid conditions was significantly higher for "high risk" pts vs "low risk" (p<0.001). The prevalence of high risk for OSA increased with increasing number of self-reported comorbid conditions; 18% with no comorbid conditions, 24% with 1 comorbid condition, 25% with 2 comorbid conditions, 37% with 3 or more comorbid conditions (p<0.001 linear-by-linear association). Prevalence of pts with a high risk of OSA was inversely associated with kidney function. Prevalence by CKD groups was 22%, 28%, 35% and 44% for CKD stage 1-2, CKD 3, CKD 4 and CKD 5 stage, respectively (p=0.004; linear-by-linear association)(Figure G-11). In the TX group, male gender, older age, use of hypnotic drugs, the presence of 3 or more comorbid conditions and lower educational status were independent and significant predictors of high risk of OSA (Table G-50).
Authors' Comments	Impaired kidney function was independently associated with high risk for OSA as was male gender, obesity and comorbidity. A similar prevalence of high risk for OSA was found for both TX and WL groups.

Table G-48. Prevalence of High Risk for OSA

	Transplanted (Tx) patients ($n = 841$)	Waitlisted (WL) patients ($n = 175$)	P value
Prevalence of high risk of OSAS: % (Number of 'high risk' patients/Number of participant patients)	27 (231/841)	33 (58/175)	0.079

Table G-49. High vs Low Risk for OSA

	High risk for OSAS ($n = 231$)	Low risk for OSAS ($n = 610$)	P value
Age (mean ± SD) (years)	52 ± 11	47 ± 13	<0.001
Male (%)	64	56	<0.05
Years of formal education: Less or equal to 8 years (%)	25	15	<0.01
Number of comorbid conditions (%): No comorbid condition as reference	16	27	<0.001
1 comorbid condition	20	23	
2 comorbid conditions	20	22	
3 or more comorbid conditions	44	28	
Diabetes (%)	22	15	<0.05
Cerebrovascular disease (%)	40	26	<0.001
Heart disease (%)	37	25	<0.001

Table G-50. Binary Logistic Regression Analysis of Correlates of High Risk for Sleep Apnea

	Odds ratio	95.0% C.I. for odds ratio		*P* value
		Lower	Upper	
Male gender	1.910	1.340	2.722	<0.001
Age (1 year increase)	1.017	1.003	1.032	0.019
Years of formal education: (More than 8 years as reference)	1.977	1.317	2.967	0.001
Less or equal to 8 years				
Groups formed by number of comorbid conditions (No comorbid condition as reference)				0.008
1 comorbid condition	1.388	0.826	2.334	0.216
2 comorbid conditions	1.384	0.820	2.335	0.223
3 or more comorbid conditions	2.156	1.354	3.431	0.001
eGFR (1 ml/min./1.73 m^2 decrease)	1.016	1.007	1.026	0.001
Serum CRP (1 mg/l increase)	1.001	0.990	1.013	0.864
Hypnotic drug use	2.705	1.429	5.120	0.002

Figure G-11. Association between the presence of high risk for sleep apnea by chronic kidney disease stage