Obesity as an effect modifier of the risk of death in chronic kidney disease

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Abstract
In the general population, obesity is associated with increased risk of end-stage renal disease (ESRD), especially if obesity occurs during young adulthood. Obesity is also associated with increased cardiovascular risk and mortality in the general population. However, observational studies which focused on populations with ESRD have demonstrated a more indirect association between body mass index and mortality, and this association has been termed paradoxical. Some have questioned whether the association between obesity and mortality is modified by ESRD. In this review, we discuss effect modification and interaction and factors that may lead to an assumption of effect modification when we observe decreased mortality among obese adults with ESRD. We show that assumptions of the existence of effect modification may be incorrect when the analysis is conditioned on a particular disease state that is influenced by obesity.

Introduction
Before the industrial revolution, obesity reflected extreme prosperity with access to meats, fruits and wine [1]. Servants performed the needed chores to maintain access to clean water and food. Thus, prosperity equated with higher caloric expenditure and decreased energy expenditure: the formula for obesity. King Henry the VIII ruled England from 1509 to 1547 and he commissioned multiple portraits of himself during this reign as king. A portrait completed circa 1535 and attributed to Joos van Cleve shows a slim king at the approximate age of 46 years. A portrait painted 5 years later by Hans Holbein, the younger, shows a stout King Henry and he likely continued to gain weight as a portrait by Hans Eworth circa 1545 reveals a perhaps morbidly obese King Henry the VIII. The king died at the age of 56, a long lifespan for the 16th century. Thus, it does not appear that obesity negatively impacted the lifespan of King Henry the VIII. One could even argue that his obesity actually contributed to his longevity.

This review examines the association between obesity and mortality among adults with chronic kidney disease (CKD) and explores whether obesity may modify the association between CKD and mortality. We show that several assumptions must be made before exploring the presence of effect modification or interaction and that issues of selection bias and confounding should be considered when observations in a population with CKD differs from what we observe in a population without CKD.

Owing to the overlay between relative prosperity and weight prior to the 20th century, obesity was not viewed as a health problem. It was not until the 20th century that companies profiting from life insurance premiums took notice of obesity and its impact on lifespan. Height-for-weight tables were created by the Metropolitan Life Insurance Company and were constructed using data from healthy (mostly white) individuals who purchased life insurance during years 1935–54 [2]. Utilization of such height for weight tables to determine life insurance premiums continues today. Table 1 shows an example of a height for weight table employed by an insurance and financial planning.
company to determine the cost an individual should expect to pay for his/her insurance premium. Although many people who are overweight or obese during midlife achieve a normal lifespan, the height for weight tables used by insurance companies predict an ~25% higher mortality risk for overweight or obese individuals compared with nonoverweight within any age group. Nonoverweight individuals are offered the lowest cost insurance premiums (Table 1).

In 1997, the World Health Organization created the obesity staging system to help identify individuals who would benefit from weight loss interventions. The ideal BMI was set at 18.5–24.9 kg/m² while overweight was defined as a BMI ≥25 kg/m². Three obesity stages were created: Stages I (BMI 30–34.9 kg/m²), II (BMI 35–39.9 kg/m²) and III (BMI ≥40 kg/m²) [3]. Studies have consistently demonstrated that obesity at a young age or during midlife decreases life expectancy [4–7]. Other studies have shown that obesity is associated with a heightened mortality risk regardless of age (through age 74), but the association between mortality risk and obesity is strongest if obesity occurs during midlife [8]. The BMI threshold indicating heightened cardiovascular risk may differ in Asian populations [9].

### Table 1. *Height for weight tables used to determine price for an insurance policy*

<table>
<thead>
<tr>
<th>Height</th>
<th>Weight (lbs)</th>
<th>Maximum weight for lowest premiums $</th>
<th>Maximum weight for standard premiums $$</th>
<th>Weight for elevated premiums $$$</th>
<th>May be declined</th>
</tr>
</thead>
<tbody>
<tr>
<td>5’4”</td>
<td>181</td>
<td>210</td>
<td>246–290</td>
<td>≥291</td>
<td></td>
</tr>
<tr>
<td>5’5”</td>
<td>186</td>
<td>216</td>
<td>246–295</td>
<td>≥295</td>
<td></td>
</tr>
<tr>
<td>5’6”</td>
<td>191</td>
<td>221</td>
<td>251–305</td>
<td>≥306</td>
<td></td>
</tr>
<tr>
<td>5’7”</td>
<td>197</td>
<td>226</td>
<td>256–210</td>
<td>≥311</td>
<td></td>
</tr>
<tr>
<td>5’8”</td>
<td>201</td>
<td>231</td>
<td>266–320</td>
<td>≥321</td>
<td></td>
</tr>
<tr>
<td>5’9”</td>
<td>206</td>
<td>236</td>
<td>271–330</td>
<td>≥331</td>
<td></td>
</tr>
<tr>
<td>5’10”</td>
<td>212</td>
<td>243</td>
<td>281–335</td>
<td>≥336</td>
<td></td>
</tr>
<tr>
<td>5’11”</td>
<td>218</td>
<td>252</td>
<td>286–345</td>
<td>≥346</td>
<td></td>
</tr>
<tr>
<td>6’0”</td>
<td>224</td>
<td>257</td>
<td>296–355</td>
<td>≥356</td>
<td></td>
</tr>
<tr>
<td>6’1”</td>
<td>229</td>
<td>264</td>
<td>301–360</td>
<td>≥361</td>
<td></td>
</tr>
<tr>
<td>6’2”</td>
<td>235</td>
<td>272</td>
<td>311–370</td>
<td>≥371</td>
<td></td>
</tr>
</tbody>
</table>

*Assumes no other comorbid condition or family history of heart disease and normal cholesterol levels. Based on weights for males–females may actually have higher rates for any given level of weight. Adapted from LLG Financial Wealth Management and Planning. [http://www.llgfinancial.com/overweight_obese.php](http://www.llgfinancial.com/overweight_obese.php) [52].

Effect modification refers to a concept that the effect of a given exposure, such as end-stage renal disease (ESRD), on an outcome, such as mortality, differs by a third factor, such as obesity. An effect modifier cannot be the result of the exposure [10]. In other words, obesity cannot be explored as an effect modifier of the association between ESRD and mortality if obesity is the result of having kidney disease. Given the reasonable assumption that obesity is not due to ESRD, obesity may be explored as a potential modifier of the association between ESRD and mortality. In what follows, we will focus on effect modification and interaction on the multiplicative scale; analogous definitions for the additive scale are also possible.

If the presence of the third factor (obesity) amplifies the effect of the exposure (kidney disease) on the outcome (e.g. mortality), then the combination of the effect modifier and exposure (obesity and kidney disease) are viewed as synergistic [11]. If the presence of the third factor mitigates the effect of the exposure on the outcome, then the effect modifier and exposure are considered antagonistic [11]. Effect modification and interaction are often equated, for example by Sklo and Nieto, who define interaction either as heterogeneity of associations across some third factor, or a departure from the expected joint effect of two factors from the observed joint effect [12]. VanderWeele has argued for a separation of the two concepts, based on directed acyclic graph criteria and marginal structural models, demonstrating that the two are identical only in situations where the exposure of interest (here, ESRD) blocks all paths between the effect modifier or interacting covariate (here, obesity) [10]. In our example, we focus on a multiplicative model but the conceptual theory is the same for risk difference measures [12]. In evaluation of a multiplicative interaction, the expected joint effect is estimated by multiplying the independent relative effects of the main exposure K...
pared with healthy lean adults [20]. Metabolically healthy shown heightened risk of coronary heart disease among obese adults have a lower mortality risk than obese adults who are not metabolically healthy [21]. However, a few studies have shown heightened risk of coronary heart disease among obese individuals compared with nonobese individuals regardless of presence of hypertension, diabetes or elevated cholesterol levels [22, 23]. Discrepancies across studies may be a function of the wide spectrum of definitions for metabolic health [24].

<table>
<thead>
<tr>
<th>BMI 18.5–29.9 (not obese)</th>
<th>No kidney disease</th>
<th>Kidney disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI ≥ 30 (obese)</td>
<td>A</td>
<td>B</td>
</tr>
</tbody>
</table>

Three factors are possible. B = relative risk of mortality for individuals with kidney disease versus no kidney disease among the non-obese, C = relative risk of mortality for obesity versus no obesity in people with no kidney disease and D = relative risk of mortality for individuals with kidney disease versus no kidney disease among the obese. Multiplicative interaction would be present if the following were true:

\[
B \times C \neq A \times D. 
\]

A few scenarios are possible. D may be much larger than \(B \times C\) which indicates synergism and \(A \times D\) may be much smaller than \(B \times C\) which indicates antagonism.

**OBESITY AND MORTALITY IN GENERAL POPULATION**

In the general population, BMI is directly associated with mortality. Associations are stronger if obesity occurs at an age <65 years versus age ≥65 years [4, 8, 13, 14]. The majority of studies which examined the association between obesity and mortality among individuals with ESRD have consistently demonstrated a U-shaped association between BMI and mortality with higher BMI associating with lower mortality compared with an ideal BMI group (18.5–24.9 kg/m²) [15–19]. A meta-analysis which included 97 studies and a sample size of 2.88 million adults showed significantly higher all-cause mortality with BMI levels ≥35 kg/m² (obesity Stages II–III) compared with the ideal BMI group (18.5–24.9 kg/m²). All-cause mortality was actually 6% lower (95% CI 0.91–0.96) among overweight individuals compared with the ideal BMI [7]. The association between obesity and mortality appears to be mediated by insulin resistance and its clinical manifestations [20, 21]. Individuals who are obese but metabolically healthy (absence of insulin resistance and/or less than two metabolic syndrome traits defined by the Adult Treatment Panel III) do not have significantly higher mortality risk compared with healthy lean adults [20]. Metabolically healthy obese adults have a lower mortality risk than obese adults who are not metabolically healthy [21]. However, a few studies have shown heightened risk of coronary heart disease among obese individuals compared with nonobese individuals regardless of presence of hypertension, diabetes or elevated cholesterol levels [22, 23]. Discrepancies across studies may be a function of the wide spectrum of definitions for metabolic health [24].
with individuals who are not obese. These differing associations between ESRD and CVD mortality by obesity status may be mediated by the \( \sim 30\% \) higher CVD mortality associated with obesity among individuals without ESRD. CVD mortality rates are also higher among the nonobese individuals with ESRD compared with the obese individuals with ESRD. The overall relative rate of CVD mortality by ESRD status, regardless of obesity was \( \sim 10.0 \).

A \( 2 \times 2 \) table can be constructed from the data in Table 2 to examine the interaction between obesity and kidney disease on CVD mortality:

### Table 2. Unadjusted incidence rates of CVD mortality among adults with and without end-stage renal disease

<table>
<thead>
<tr>
<th></th>
<th>Incidence rate</th>
<th>Relative rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted incidence rates of CVD mortality</td>
<td></td>
</tr>
<tr>
<td>BMI ≥30 kg/m(^2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESRD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI 18.5–29.9 kg/m(^2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESRD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from de Mustert et al. [28].

In this situation, \( B \times C \neq A \times D \) so we can state a multiplicative interaction is present. Similar findings were noted for all-cause mortality but the differences in the relative rates for ESRD by obesity status were smaller. As stated previously, the authors stated that the hazard ratios for all-cause mortality by obesity status (BMI ≥30 kg/m\(^2\)) relative to a BMI 22.5–25.0 kg/m\(^2\) were similar across populations with and without ESRD. Table 3 shows the relative rates for CVD mortality and all-cause mortality for the BMI categories compared with referent group 22.5–25.0 kg/m\(^2\) by ESRD status. In this table, one can see that the BMI group 25–27.5 kg/m\(^2\) had the largest difference in relative rates of CVD mortality between groups with and without ESRD. Compared with the referent BMI group 22.5–25.0 kg/m\(^2\), the BMI group 25–27.5 kg/m\(^2\) shows substantially lower CVD mortality in the group without ESRD but not in the group with ESRD. These incidence rates are unadjusted but the study did restrict the study populations to the age range 50–75 years.

### DOES OBESITY MODIFY THE EFFECTS OF ESRD ON MORTALITY?

The fact that the association between BMI and mortality differs in populations with and without ESRD has been called paradoxical [29]. Can this paradox be framed in terms of effect modification or interaction? As stated before, we cannot view obesity as the main exposure and kidney disease as the effect modifier, but we can view kidney disease as the main exposure for mortality risk and obesity as the third factor which may modify the effects of kidney disease on mortality. This would allow us to stratify high- and low-risk ESRD patients, and potentially devote more resources to those at higher risk. However, an effect modifier is considered something that only indicates a higher or lower risk and is not itself modifiable. If the goal is to determine appropriate interventions for obesity, we need to identify a joint effect or interaction between ESRD and obesity [10]. The identification of effect modification may be problematic, however, in the setting of competing risk. Figure 1 shows a directed acyclic graph of plausible causal relationships between obesity, CKD, ESRD and death. Effect modification of the association between ESRD and mortality by obesity status may be difficult to elucidate due to competing risk of non-ESRD mortality. Non-ESRD mortality may be due to the direct effects of obesity and other unmeasured factors and occurs before ESRD is reached. If competing risks for ESRD along with unmeasured factors that influence both obesity and CKD could be taken into account, then effect modification by obesity may be identified. Such information could help identify patients with the highest risk for ESRD mortality based on obesity status.

### CONFOUNDED VERSUS CAUSAL ASSOCIATIONS

Before exploring effect modification, one first must confirm that the association between the main exposure and the
outcome is not due to confounding. The link between obesity and cardiovascular outcomes and mortality has been determined through observational studies. In other words, we observe mortality risk among individuals who are obese and we observe mortality risk among individuals who are not obese. These risks are then compared to determine a risk difference or relative risk by presence of obesity. Observing what happens is really limited by our window of observation. In a perfect observational study, we would observe an individual with an ideal BMI for a given period of time and examine their longevity and cause of death. Then we would observe the same exact individual during the same exact time period for the same length of time except during this observation the individual is obese. We then follow this person over time to see how long they live and determine their cause of death. If lifespan was shorter when obesity was present compared with when obesity was not present, then we could be certain of a causal influence of obesity on mortality. This scenario may be viewed as counter-factual because such a situation would never occur. Only the counterfactual observation would provide the absolute true association between obesity and mortality [30]. Instead, we compare our observations of individuals with kidney disease who are obese with our observations of individuals with kidney disease who are not obese. Statistical modeling may be used to control for factors that are measured such as age, sex, race/ethnicity and comorbid conditions. Other factors such as social measures, dietary practices and physical activity patterns are not well measured—if at all—in most observational studies. Controlling for factors that are poorly measured may actually introduce bias to any analysis.

A confounder is defined by a variable that is associated with both the exposure and the outcome but does not mediate the association between the exposure and the outcome [12]. Before exploring interaction, the analysis must address any potential confounding. The choice of a statistical model is dictated by pragmatism [12], and one can only adjust for covariates available to the investigator. Given the 10-fold higher mortality rates among individuals with ESRD compared with the general population [28], it is not likely that this robust association is due to confounding. However, the apparent protective associations reported between obesity and mortality among adults with ESRD is not robust [15, 17, 29] and may not be causal but rather a function of confounding.

One of the largest studies to examine obesity and mortality included over 400 000 dialysis patients who initiated dialysis from 1995 to 2000 [15]. This study reported substantial and significant differences in overall survival by BMI groups after a median follow-up of 2 years. Cardiovascular diseases including ischemic heart disease, myocardial infarction, peripheral vascular disease, previous stroke were all lowest in the group with a BMI ≥ 37 kg/m². After adjustment for these factors, BMI categories starting at a BMI ≥ 25 kg/m², including the highest BMI category (≥ 37 kg/m²), were associated with decreased mortality compared with BMI 22 to <25 kg/m². The highest mortality was noted in ESRD patients with a BMI <22 kg/m² [15]. When the investigators restricted the analysis to incident dialysis patients who had previously received a transplant, a potentially healthier group compared with the entire ESRD population, increased mortality was again noted among patients with BMI <22 kg/m². However, increased mortality was now noted among those with BMI ≥ 37 kg/m² compared with the BMI group 22 to < 25 kg/m² [31]. Thus, morbid obesity did not appear to be protective among ‘healthier’ ESRD patients. Hoogeveen et al. [32] also showed that if the

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>CVD mortality</th>
<th>All-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence rate</td>
<td>Relative rate</td>
</tr>
<tr>
<td>ESRD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.5–22.5</td>
<td>10.2</td>
<td>1.27</td>
</tr>
<tr>
<td>22.5–25.0</td>
<td>8.0</td>
<td>1.00 (referent)</td>
</tr>
<tr>
<td>25–27.5</td>
<td>9.4</td>
<td>1.17</td>
</tr>
<tr>
<td>27.5–30</td>
<td>7.6</td>
<td>0.95</td>
</tr>
<tr>
<td>≥30</td>
<td>7.3</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Table 3. Crude incidence and relative rates of CVD and all-cause mortality by BMI groups and by end-stage renal disease status

Adapted from de Mustert et al. [28].

Effect modification and ESRD
An additional consideration when assessing whether obesity modifies the association between ESRD and mortality is competing risk. Analyses that focus on populations with CKD are conditioned on a unique outcome ESRD. Given the fact that prevalence of CKD exceeds ESRD by over 20-fold [33, 34], development of ESRD must be viewed as an uncommon event while death before ESRD must be more common. If an individual dies before developing kidney failure, then the age of ESRD initiation is never observed. The unobserved age of ESRD initiation can be viewed as missing, and the analyses needs to account for this missing data [35]. This lack of information may lead to a form of selection bias; we are unable to observe what would have happened if the patient survived. In the ESRD population, obese individuals are generally younger than the nonobese individuals. This is likely due to the fact that obesity at a young age is strongly associated with ESRD [36]. In a study of 320,252, adults aged 18–34 years enrolled in the Kaiser Permanente health system who volunteered for a screening health checkup between 1964 and 1985, those with a baseline BMI $\geq 35$ and $\geq 40$ kg/m$^2$ had an approximate 500 and 600% higher risk of ESRD, respectively, when compared with those with a baseline ideal BMI (18.5–24.9 kg/m$^2$). In the study of obesity and mortality which included over 400,000 dialysis patients who initiated dialysis from 1995 to 2000, the average age of patients with BMI $\geq 37$ kg/m$^2$ was 56.7 years while the average age of individuals in the ideal BMI range 22.0–24.9 kg/m$^2$ was 62.3 years. Age decreased linearly across increasing BMI groups [15].

The 100% higher relative risk of mortality associated with obesity versus an ideal BMI during young adulthood may be viewed as weak [8] compared with the 500–600% higher relative risk of ESRD associated with morbid obesity versus an ideal BMI [36]. Because individuals with morbid obesity likely initiate ESRD at a younger age compared with nonobese individuals, these individuals will remain on dialysis for a longer period of time compared with nonobese patients. Such examples include hypertension associated kidney disease whereby obesity may influence kidney disease progression [37, 38]. In the African American Study of Kidney Disease which included 691 African Americans with hypertension-associated kidney disease, the mean age of the participants at the start of the cohort phase was 54.6 years and mean BMI was 31.4 kg/m$^2$. After 11 years of follow-up, the AASK participants were 5-fold more likely to initiate ESRD than to die of cardiovascular disease [39]. The fact that these individuals were more likely to develop ESRD rather than die is likely a function of their young age at study start.

Another major issue when assessing obesity and mortality is the method of assessing obesity. Abdominal obesity likely plays a role in both CKD incidence and progression [31, 38, 40, 41] and may also influence cardiovascular risk and mortality [42, 43]. Several studies have reported that a high BMI is either protective for cardiovascular events and mortality or that BMI is not associated with cardiovascular events or mortality among individuals with CKD [31, 44, 45]. Among 1669 adults with an estimated glomerular filtration rate 59–14 mL/min/1.73 m$^2$, no significant association was noted between overweight (BMI 25.0–29.9 kg/m$^2$) or obesity ($\geq 30$ kg/m$^2$) and cardiac events when compared with a BMI 20–24.9 kg/m$^2$ after an average of 9.3 years of follow-up [31] However, risk of myocardial infarction or cardiovascular death was significantly higher among those with the highest waist-hip ratio ($\geq 1.02$ and 0.96 in men and women, respectively) compared with the group with the lowest waist-hip ratio ($\leq 0.95$ and 0.87 in men and women, respectively) [31]. Others have also shown a significant and linear association between waist circumference and mortality among adults with CKD. Among 5805 adults with CKD, defined as an elevated spot urine albumin/creatinine ratio or an estimated glomerular filtration rate $<60$ mL/min/1.73 m$^2$, BMI 18.5–24.9 kg/m$^2$ and BMI $>35$ kg/m$^2$ were associated with significantly higher mortality risk compared with a BMI 25–29.9 kg/m$^2$. However, after adjustment for waist circumference, only the BMI group 18.5–24.9 kg/m$^2$ remained significantly associated with mortality compared with
the referent group while BMI >35 kg/m$^2$ did not [43]. In contrast, mortality risk increased in a linear fashion across increasing waist circumference categories after adjustment for BMI and other covariates [43]. Another study which focused on 537 patients receiving dialysis in Italy, every 1 kg/m$^2$ increase in BMI was associated with an 11% decrease in mortality while every 10-cm increase in waist circumference was associated with a 23% (95% CI 1.02–1.47) increase in all-cause mortality. Similar findings were noted for cardiovascular mortality [42]. These findings are consistent with multiple studies which show a direct and linear association between waist circumference and mortality risk after adjustment for BMI in general populations [46–48].

Although BMI remains the most common method for obesity assessment and staging, numerous alternatives for obesity assessment exist. Such alternatives include the conicity index, the waist–hip ratio and bioimpedance analysis [49, 50]. It should be noted that clinical guidelines for obesity assessment in the general population suggest consideration of both BMI and waist circumference to determine a patient’s adiposity-related disease risk and to guide obesity management [51]. Thus, the medical community should not focus solely on BMI to determine health-related risks associated with obesity among adults with CKD.

**CONCLUSION**

In conclusion, caution should be taken when interpreting the presence of effect modification or interaction. In an observational study, the study population observed may be influenced by selection bias, and this is likely operational when determining the impact of obesity in ESRD where obesity is in the causal pathway for ESRD development. Before exploring effect modification, confounding should be addressed, and this may be difficult if confounders are not accurately measured. Finally, the definition of obesity needs to be considered. Future studies should use both waist circumference and BMI to address the association between adiposity and mortality in a given study population.

**CONFLICT OF INTEREST STATEMENT**

None declared.

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