

Childhood Socioeconomic Status, Comorbidity of Chronic Kidney Disease Risk Factors, and Kidney Function Among Adults in the Midlife in the United States (MIDUS) Study

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Abstract

Background: There is a lack of empirical effort that systematically investigates the clustering of comorbidity among known risk factors (obesity, hypertension, diabetes, hypercholesterolemia, and elevated inflammation) of chronic kidney disease (CKD) and how different types of comorbidity may link differently to kidney function among healthy adult samples. This study modeled the clustering of comorbidity among risk factors, examined the association between the clustering of risk factors and kidney function, and tested whether the clustering of risk factors was associated with childhood SES.

Methods: The data were from 2,118 participants (ages 25-84) in the Midlife in the United States (MIDUS) Study. Risk factors included obesity, elevated blood pressure (BP), high total cholesterol levels, poor glucose control, and increased inflammatory activity. Glomerular filtration rate (eGFR) was estimated from serum creatinine, calculated with the CKD-EPI formula. The clustering of comorbidity among risk factors and its association with kidney function and childhood SES were examined using latent class analysis (LCA).

Results: A five-class model was optimal: (1) **Low Risk** (class size = 36.40%; low probability of all risk factors), (2) **Obese** (16.42%; high probability of large BMI and abdominally obese), (3) **Obese and Elevated BP** (13.37%; high probability of being obese and having elevated BP), (4) **Non-Obese but Elevated BP** (14.95%; high probability of having elevated BP, hypercholesterolemia, and elevated inflammation), and (5) **High Risk** (18.86%; high probability for all risk factors). Obesity was associated with kidney hyperfiltration, while comorbidity between obesity and hypertension was linked to compromised kidney filtration. As expected, the High Risk class showed the highest probability of having $eGFR < 60 \text{ ml/min/1.73 m}^2$ ($P = .12$; $95\%CI = .09 - .17$). Finally, low childhood SES, controlling for education, adult SES, age, gender, and race, was associated with a higher probability of being in the High Risk rather than the Low Risk class ($b = -0.20$, $SE = 0.07$, $OR [95\%CI] = 0.82 [0.71-0.95]$).

Conclusion: These results highlight the importance of considering the impact of childhood SES on risk factors known to be associated with chronic kidney disease.

Background

The risk for Chronic Kidney Disease (CKD) is heightened among individuals with risk factors, including obesity, hypertension, diabetes, hypercholesterolemia, and elevated inflammation [1-5]. Comorbidity among these risk factors is common and often leads to a faster progression to CKD [2, 6]. Different characteristics of comorbidity among these risk factors may link to a different state of kidney functioning. For example, in the early stage of obesity when hypertension is absent, obese individuals show elevated kidney filtration as a sign of an early adaptive process to hemodynamic changes due to obesity [6, 7]. On the other hand, comorbidity between obesity and hypertension indicates a further progression of damages in kidney structures and thus progressive declines in kidney function [6-8]. Multiple mechanisms have been shown through which obesity link to hypertension and CKD, including hypercholesterolemia, hyperglycemia, and inflammation [6]. However, there is a lack of empirical effort that systematically investigates the clustering of comorbidity among these risk factors and how different types of comorbidity may link differently to kidney functioning among healthy adult samples. This knowledge is important for prevention efforts on lowering the risk of progression to CKD by recognizing and further treating the risk factors and their comorbidity [2].

Contextualizing the Heterogeneity of Risk Factors

Integral to the prevention effort of CKD is contextualizing the clustering of comorbidity among risk factors, which means understanding social factors that associated with differentiation in the development and variations in the clustering among these risk factors. Socioeconomic status (SES) is an important social factor associated with the risk factors. SES is a general term for group of valued resources, comprising both economic or material resources and also prestige or social status [9]. The burden of CKD is not evenly distributed in the population as the prevalence of CKD is higher among individuals from lower levels SES [10]. The socioeconomic disparities in CKD has been shown to be mediated by each of the risk factors including obesity, hypertension, diabetes, hypercholesterolemia, and inflammation [5, 11]. However, there is a lack of empirical studies that examine the association between SES and the clustering among CKD risk factors.

Furthermore, SES is a dynamic concept in which its influence on health may span across different

developmental stages across the life course [12, 13]. Throughout the life course, there are at least three important periods in which one's SES may have significant impact on health [14-16]: 1) SES during childhood as determined by one's parental SES, 2) formal education attainment throughout early adulthood that may influence one's future social and economic prospect across adulthood, and 3) current SES in adulthood, reflected by level of income and social status. Recently, there have been more interests in documenting the influence of childhood SES on the development of kidney disease and its risk factors [13, 17, 18]. Multiple studies have documented a significant influence of socioeconomic adversity during childhood on the emergence and presentation of disease in adulthood [19, 20]. Our analysis focused on the potential association between childhood SES and risk factors associated with CKD. Childhood SES may initiate the developmental trajectory toward CKD in adulthood by influencing the development and comorbidity of the risk factors. Previous studies have shown that low childhood SES, independent of education level and current level of SES (e.g., income), was associated with higher likelihood of obesity [21, 22], elevated BP [23, 24], diabetes [25, 26], and elevated inflammatory physiology [27, 28] later in adulthood. However, our understanding is limited when it comes to the association between childhood SES and comorbidity of these risk factors and how comorbidity of risk factors may be associated with kidney function across adulthood.

Methods

Participants and Procedure

Data for this study are from the Midlife in the United States (MIDUS) study, a national study of health and well-being involving a national probability sample of middle and older adults from the 48 continental states [29]. MIDUS was started in 1995-1996 (MIDUS 1), included 7,108 adults, ages 25-74, recruited through random digit dialing (RDD) and completed baseline telephone interview.

Majority of the participants (89% of the total sample) in MIDUS 1 were also completed self-administered questionnaires (SAQ). The longitudinal follow-up of MIDUS was conducted in 2004-2006 (MIDUS 2), included 4,963 longitudinal participants. Similar to MIDUS 1, all the participants in MIDUS-2 completed the baseline telephone interview, in which 81% of them also completed the SAQ. To increase the racial diversity of MIDUS 2 sample, a supplemental sample consisted majority Black

adults was recruited from Milwaukee County, WI ($n = 592$). Similar to the national sample in MIDUS 2, all the Milwaukee supplemental also completed baseline interview and majority of them (89% of the total sample) completed the SAQ. A new protocol of biomarker assessment was introduced during MIDUS 2. Participants who completed both baseline telephone interview and SAQ were eligible to participate in the biomarker assessment. In MIDUS 2, 1,255 randomly selected participants, both from the national sample and the Milwaukee supplemental sample, completed the biomarker assessment. In 2012–2016, a new national probability sample ($n = 3,577$) that matched the original MIDUS sample (MIDUS 1) in terms of their sociodemographic characteristics was recruited to participate in the MIDUS Refresher study (MIDUS R). This sample was recruited to replenish the number of middle-aged adults given that the initial cohort was now older [14, 30]. Similar to MIDUS 1 and 2, participants in MIDUS R were recruited through RDD and all completed the baseline telephone interview. Majority of the participants in MIDUS R (73%) also completed the SAQ. Similar to MIDUS 2, a supplemental sample was also recruited from Milwaukee County in order to increase the racial diversity of the sample in MIDUS R ($n = 508$). Among the supplemental sample in MIDUS R, 299 participants (59% of the in-person interview participants) completed the SAQ. MIDUS R also include biomarker assessment protocol, with the same eligibility requirement as in MIDUS 2 (completed the baseline survey and SAQ). In MIDUS R, 863 participants (randomly selected from the national sample and the Milwaukee supplemental sample) completed the biomarker assessment.

For the current analysis, data were from 2,118 (ages 25–84; 54.9% female; 73.7% non-Hispanic White) participants who completed the biomarker assessment in MIDUS 2 and MIDUS R. The biomarker assessment protocol in MIDUS 2 and MIDUS R was identical. Participants were invited to stay overnight at one of the three regional clinical research units (CRUs; West Coast, Midwest, and East Coast). The selection of the CRU for each participant was based on the one that imposed the least travel burden. Blood and urine samples were collected during the stay. Participants provided informed consent to participate in both the baseline survey and the biomarker assessment. Additional information regarding biomarker assessment in MIDUS study can be found elsewhere [31].

Measures

Risk Factors

Seven known risk factors for CKD were included in this analysis: (1) elevated blood pressure/ BP (mean of second and third blood pressure test: systolic and diastolic blood pressure $\geq 140/90$ mmHg or self-reported diagnosis of hypertension by physician; (2) elevated glycosylated hemoglobin (HbA1c $\geq 6.5\%$) or high fasting blood glucose (≥ 126 mg/dL) or self-reported diagnosis of type 2 diabetes by physician; (3) obese (BMI ≥ 30 kg/m²); (4) abdominal obesity (waist circumference ≥ 88 cm for women and ≥ 102 cm for men); (5) hypercholesterolemia (total serum cholesterol ≥ 200 mg/dL); (6) elevated c-reactive protein (CRP \geq the third quartile); and (7) elevated interleukin 6 (IL6 \geq the third quartile).

Kidney Function

Estimated glomerular filtration rate (eGFR) was estimated from serum creatinine using the CKD-EPI formula [32]. Serum creatinine was assayed from overnight fasted blood collected at the three CRUs using Roche Cobas Analyzer (Meriter Clinical Lab, Madison, WI; inter-assay coefficient of variability = 2.08%). The overall mean of eGFR was 91.2 mL/min/1.73 m² (*SD* = 19.2 mL/min/1.73 m²). For further analysis, eGFR was transformed into a binary variable based on the clinical indicator of Stage 3 CKD (1 = eGFR lower than 60 ml/min/1.73 m², *n* = 107 [5.1%]; 0 = the rest of participants).

Childhood SES

Childhood SES was the total score from three indicators, including (1) father (or mother in case of missing data) highest level of education (0 = < high school, 1 = graduated from high school/GED, 2 = some college or higher); (2) whether family of origin received welfare (0 = all the time/most of the time, 1 = some of the time/a little of the, 2 = never in welfare); and (3) financial level growing up (0 = a lot/somewhat/a little worse off than average family, 1 = same as average family, 2 = a lot/somewhat, a little better off than average family). The mean childhood SES score was 3.91 (*SD* = 1.45; range = 0 - 6). These measures of childhood SES has been shown to be a significant predictor of health outcomes in adulthood, such as allostatic load, chronic disease, and diabetes [14, 33, 34].

Covariates

Covariates in the analysis include participant's highest formal education level (0 = no high school

diploma/ GED; 1 = graduated from high school and higher) and current/ adult SES. Adult SES was the total score based on five indicators [14, 33, 34], including: (1) household-size adjusted income to poverty ratio (0 = < 150%, 1 = \geq 150% - < 300%, 2 = \geq 300%); (2) current financial situation (0 = worse, 1 = average, 2 = best); (3) availability of money to meet basic needs (0 = not enough money, 1 = just enough money, 2 = more money than need); and (4) difficulty level paying bills (0 = very/somewhat difficult, 1 = not very difficult, 2 = not at all difficult). Sociodemographic variables were also incorporated as covariates, including age (years), gender (female = 0, male = 1), and race/ ethnicity (minority = 0, non-Hispanic White = 1).

Statistical Analysis

Using a national probability sample of the U.S. adults, the following analysis had three primary aims (Figure 1): (1) to model the heterogeneity of comorbidity among CKD risk factors by examining the clustering of risk factors associated with age-related declines in kidney function among middle-aged and older adults; (2) to empirically test whether the clustering of comorbidity among CKD risk factors link to kidney function as a proof of concept that different characteristics of comorbidity are associated with different state of kidney functioning; and (3) to contextualize the different clustering of CKD risk factors by testing whether childhood SES, controlling for education, adult SES, age, gender, and race, was associated with the heterogeneity of comorbidity of CKD risk factors. Latent class analysis (LCA) was employed to address these research questions. A person-centered analysis such as LCA provides objective and parsimonious solutions regarding the variation in the clustering of risk factors, its impact on kidney function, and prediction by childhood SES. The analysis was divided into three steps. First, we identified the heterogeneity of the comorbidity among risk factors. Second, we examined the association between latent classes of risk factors and kidney function. Third, we tested the evidence whether childhood SES was associated with the heterogeneity of comorbidity among CKD risk factors by utilizing model-based approach LCA.

Step 1: Examination of the Heterogeneity of Comorbidity Among Risk Factors

Selection of the optimally fitting model was based on model fit statistics and selection criteria,

parsimony principle, as well as theoretical interpretability. Model fit statistics and selection criteria included the Akaike information criterion (AIC), Bayesian information criterion (BIC), sample-size adjusted BIC (a-BIC), entropy, Bozdogan's consistent AIC (CAIC), and bootstrapped likelihood ratio test (BLRT). A better fit model is indicated by lower values for the AIC, BIC, and a-BIC. In addition, higher values for entropy indicated higher classification utility. Finally, significant p -values of bootstrapped likelihood ratio test indicated improved model fit compared to models with one fewer class. Two, three, four, five, and six latent classes LCAs were compared to select the best fitting model. Model identification was conducted by using 1,000 sets of random starting values; all models were estimated using PROC LCA on SAS [35]. Two sets of parameters are of most interest from the best fitting model. The first set is the latent class membership probabilities, which indicate the distribution of the classes in the population. The second set is the item-response probabilities, which indicate the probabilities of providing certain responses to observed variables conditional on class membership [35]. These two sets of parameters are used to label and interpret the classes. The analysis was conducted using PROC LCA on SAS [35].

Step 2: Testing the Association Between the Heterogeneity of Comorbidity Among Risk Factors and Kidney Function

In the second step, we examined whether latent classes of CKD risk factors were predictive of eGFR. We used eGFR as both continuous and binary variable ($1 = < 60 \text{ ml/min/1.73 m}^2$, $0 = \geq 60 \text{ ml/min/1.73 m}^2$). For the analysis with eGFR as a continuous variable, the outcome from the analysis was the expected mean of eGFR for each latent class of CKD risk factors. When predicting eGFR as a binary variable, the outcome of the analysis indicated the probability of having eGFR lower than $60 \text{ ml/min/1.73 m}^2$ for each latent class. We utilized LCA with a distal outcome to test this hypothesis using the BCH approach [36]. The LCA with a distal outcome was executed using LCA_Distal_BCH SAS macro [37].

Step 3: Examining the Association Between Childhood

SES and the Heterogeneity of Risk Factors

In the final step of the analysis, we examined whether childhood SES was associated with class membership, after controlling for education level, current SES, age, gender, and race. We tested the hypothesis by utilizing model-based approach LCA with covariates [35], in which childhood SES (score) was utilized to predict the probability of belonging to certain latent class of risk factors comorbidity (relative to the reference class), controlling for the covariates. The results were presented as the odds ratios of belonging to a certain class compared to the reference class. The model-based approach LCA was conducted using PROC LCA on SAS [35].

Missing Data

Parameters in PROC LCA are estimated by maximum likelihood using an EM (expectation-maximization) procedure [35]. This procedure handled missing data when identifying the latent class indicators, assuming that data missing at random (MAR) [35].

Results

Descriptive Statistics

Descriptive statistics for the participants in the current study are presented in Table 1. More than half of the participants in this study fulfilled the criteria of having elevated BP, abdominally obese, and hypercholesterolemic. Slightly more than half of the participants showed healthy level of kidney function ($eGFR \geq 90$ ml/min/1.73 m²). The proportion of participants with $eGFR < 60$ ml/min/1.73 m² was around 5%. In terms of childhood SES, around one-third of the participants reported that their parent did not finish high school. Similarly, almost one-third of the participants also reported that their families' financial status during their childhood were low compared to other families around them.

The Clustering of Risk Factors

Information regarding model fit statistics and selection criteria is presented in Table 2. Models with 1–6 classes were tested; the 4-class model showed lower level of BIC and CAIC (Table 2). However, the 5-class model showed better fit based on AIC and aBIC. The bootstrapped likelihood ratio test showed that 5-profile model was the last model with a significant p value. Thus, moving from the 5-class model to the 6-class model did not significantly improve the model fit. Entropy ranged from .59 (2-

profile model) to .76 (6-profile model), with values for larger classes in the mid-to-upper .70s.

Therefore, we considered models with 4 or 5 profiles. Closer examination indicated that an additional class in the 5-profile model show a non-repetitive, meaningful, and interpretable class. Thus, we selected the 5-profile model for theoretical explanation and distal outcome analysis.

Table 3 provides information pertaining to latent class membership probabilities and item-response probabilities for the 5-class model. Class 1 was labeled *Low Risk* (class size = 36.40), characterized by low probabilities for all the CKD risk factors. Class 2 was labeled as *Obese* (16.42%) given that this group of individuals had a high probability of being obese. Class 3 was identified as *Obese and Elevated BP* (13.37%) because these adults had elevated probabilities for having elevated BP with hypercholesterolemia in addition to being obese. Class 4 was characterized as *Non-Obese but Elevated BP* (14.95%). They were distinguished by high probabilities for elevated BP, hypercholesterolemia, and elevated CRP, but without indications of extreme adiposity. The final class was delineated as *High Risk* (18.86%), characterized by high probabilities for all identified risk factors.

The Association Between Latent Classes of Comorbidity Among Risk Factors and Kidney Function

The distal outcome analysis indicated that class membership was associated with eGFR (Wald $\chi^2(4) = 44.04, p < .001$). The Obese class had the highest expected mean of eGFR (99.77 ml/min/1.73 m², SE = 1.70 ml/min/1.73 m²), followed by the Low Risk ($M = 93.05, SE = 0.69$), the High Risk ($M = 88.97, SE = 1.53$), the Non-Obese but Elevated BP ($M = 85.45, SE = 1.6$), and the Obese and Elevated BP ($M = 85.43, SE = 1.71$). The association between class membership and kidney function was more apparent when considering eGFR as a binary variable (0 = eGFR ≥ 60 mL/min/m², 1 = eGFR < 60 mL/min/m²; Figure 2). The results showed that class membership was associated with different probability of having eGFR < 60 ml/min/1.73 m² (Wald $\chi^2(4) = 23.66, p < .001$). The High Risk class showed the highest expected probability ($P = .12$; 95% CI = .09 -.17) while the Low Risk showed the lowest expected probability ($P = .01$; 95% CI = .006 -.03) of having eGFR < 60 ml/min/1.73 m². The expected probabilities for the rest of the classes are as follow (lower to higher): Obese ($P = .03$; 95%

CI = .01 -.09), Obese and Elevated BP ($P = .05$; 95% CI = .02 -.11), and Non-Obese but Elevated BP ($P = .11$; 95% CI = .07 -.16). Pairwise comparisons indicated that the expected probability of having eGFR < 60 ml/min/1.73 m² for the High Risk (Wald χ^2 (1) = 20.81, $p < .050$) and Non-Obese but Elevated BP (Wald χ^2 (1) = 13.43, $p < .050$) class was significantly higher than the probability for the Low Risk class (Bonferroni correction applied for multiple comparison).

The Association Between Childhood SES and the Latent Classes of Comorbidity Among Risk Factors

Childhood SES was significantly associated with latent class membership of risk factors, even after controlling for covariates (Table 4; χ^2 [4] = 15.28, $p < .01$). Lower childhood SES was significantly associated with higher probability of being in the Obese and Elevated BP ($\beta = -0.22$, $SE = 0.07$, OR [95%CI] = 0.81 [0.70-0.93]) rather than the Low Risk class. Furthermore, Lower childhood SES was also significantly associated with higher probability of being in the High Risk ($\beta = -0.20$, $SE = 0.07$, OR [95%CI] = 0.82 [0.71-0.95]) rather than the Low Risk class. For every 1 point lower in childhood SES score, participants were 23% more likely to be in the Obese and Elevated BP class and 22% more likely to be in the High Risk class, rather than the Low Risk class. However, childhood SES was not significantly associated with the probability of membership in the Obese ($\beta = 0.09$, $SE = 0.09$, OR [95%CI] = 1.09 [0.91-1.31]) and Non-Obese but Elevated BP ($\beta = -0.10$, $SE = 0.08$, OR [95%CI] = 0.91 [0.77-1.06]) classes relative to the Low Risk class.

Discussion

The goal of this study was to examine the multiple characteristics of comorbidity among CKD risk factors using a national probability sample of healthy middle and older adults in the United States. As expected, the majority of participants in this survey would be considered to be otherwise healthy (36.40%) and had low probabilities of evincing all risk factors. However, almost one-fifth of middle-aged and older adults were found to be members of the High Risk class, which was characterized by a high probability of evincing all the assessed risk factors. The rest of the participants met the criteria for being obese or show elevated BP or exhibiting comorbidity of both obesity and elevated BP. Individuals in the Obese class showed elevated eGFR while comorbidity between obesity and elevated

BP tended to lower eGFR. In addition, the High Risk class was associated with the highest probability of having eGFR < 60 ml/min/1.73 m². Finally, childhood SES was associated with class membership of comorbidity of risk factors for CKD, independent of education level, current SES, age, gender, and race. Low childhood SES was significantly associated with higher probability of being in the Obese and Elevated BP class and High Risk class rather than the Low Risk class.

Clustering of Risk Factors and eGFR

Among the five latent classes, the Obese class had the highest expected mean of eGFR, even higher than the Low Risk class, which might initially seem to be counterintuitive. However, there is an established knowledge regarding the association between obesity and hyperfiltration in the kidney. The mechanism behind kidney hyperfiltration among obese individuals is caused by vasodilation of kidney afferent arterioles and increased glomerular hydrostatic pressure [38, 39]. Vasodilation of kidney afferent arterioles among obese individuals is especially caused by dysregulation of the tubuloglomerular feedback (TGF) mechanism (see [7] for details) that control the balance between sodium input and output. Dysregulation of the TGF mechanism in the kidney leads to increased sodium reabsorption in the tubules among obese individuals [38, 39]. Higher sodium reabsorptions in the tubules lead to a decrease in sodium concentration at macula densa, cause kidney afferent arterioles vasodilation, that in turn will increase renal blood flow, GFR, and systemic blood pressure. Multiple mechanisms are also involved in the context of excessive tubular sodium reabsorptions among obese individuals, including [39, 40]: 1) kidney compression, 2) the overactivation of the renin-angiotensin-aldosterone system (RAAS), and 3) overactivation of kidney mineralocorticoid receptor (MR).

The altered TGF mechanism due to an increase in sodium reabsorption at the kidney tubules may be adaptive at first on balancing sodium intake and output among obese individuals. However, this effort in balancing sodium is achieved at the cost of elevating blood pressure. Increase BP will eventually elevate glomerular hydrostatic pressure that in the long run will cause kidney damage [39, 40]. As indicated by our findings, membership in the Obese and Elevated BP class was associated with having the lowest expected mean of eGFR when compared to other classes. This difference is suggestive of a

progressive decrement in kidney function over time as obese adults develop chronically elevated BP, reflects the important age-related association between cardiovascular and renal physiology. A previous study found that obese individuals experienced a more rapid decrease in kidney function over time, especially among older individuals [41]. Hypertension and dyslipidemia are clinical warning signs for obese individuals that their kidney function will become compromised [42]. The eGFR for the majority of participants in the Obese and Elevated BP class would meet the clinical criterion for Stage 2 CKD. The MIDUS 2 participants are currently being reevaluated approximately 10 years after the prior assessment so there will be an opportunity to formally test if individuals from Obese class have transitioned to the Obese and Elevated BP class over time.

The High Risk class was the only category that had a high probability of also having a glycosylated hemoglobin levels indicative of type 2 diabetes. While this class generally had a higher mean eGFR when compared to the Obese and Elevated BP class, membership in this class was associated with the highest probability of meeting eGFR indicative of Stage 3 CKD. The dual impact of central adiposity and insulin resistance in the High Risk adults would be in keeping with the view that obesity is the gateway condition [43] that precedes many chronic health conditions including diabetes, cardiovascular disease, and CKD. The Non-Obese but Elevated BP class also provided distinctive insights because it reaffirms the important bidirectional relationship between renal clearance and blood pressure even in the absence of frank obesity. Membership in this class was characterized by a higher percentage of older participants. Given prior findings on the important influence of subclinical inflammatory activity [5], their lower kidney function may also be indicative of contributory effects of cytokines and other factors that can dysregulate and accelerate the aging of the kidney. There has also been some discussion about whether the criterion for Stage 3 CKD should be modified in the elderly patient because some degree of renal decline is a normal part of aging [42].

Childhood SES, Risk Factors, and Kidney Function

While several studies have previously shown the association between adult SES and risk factors for CKD [11], the current analysis documented the important influence of childhood SES on the different characteristics of clustering among CKD risk factors. The significant influence of childhood SES, after

controlling for education, current SES, age, gender, and race, indicated that the variances in the clustering of CKD risk factors were not totally explained by contemporaneous adult behavior and social standing. It reaffirms the importance of early life as a critical period for establishing the developmental trajectory to disease in adulthood.

While we do not have information regarding socioeconomic conditions during pregnancy and indicators for IUGR such as low birth weight or prematurity, the childhood socioeconomic measures that we used (e.g., parental education) are reliable indicators that reflect adversity during pregnancy and early postnatal linked to early life disease programming. Parental education, for example, has been linked to factors associated with IUGR, including undernutrition/ malnutrition, maternal disease (e.g., hypertension, diabetes), and toxic exposure (e.g., smoking, alcohol, drugs) [20, 44-48].

Limitations and Future Directions

Several limitations of this study should be acknowledged. First, our findings were based on cross-sectional data. Thus, all the results are purely associational, even though our interests involve developmental link between variables across the life course. Second, the information on childhood SES was based on retrospective self-report, which could introduce some recall bias. Although a separate examination of some participants who had siblings in the MIDUS project, including identical and fraternal twins, indicated a high concordance on the recall of childhood SES [49]. Third, the latent classes of CKD risk factors were treated similarly and as homogenous across age, sex, and racial groups. Given that each of these factors is known to influence kidney function, future analyses should formally test the heterogeneity of CKD risk factors within each of the subgroups. Although a large bias due to race would not be likely to have accounted for the overall conclusions given that both white and black Americans were represented in this study, it is likely that the magnitude of the associations could be different in other racial groups. For example, a prior analysis had shown that there are differences in the age-related decline in GFR between American and Japanese adults [5].

Another consideration is that only the CKD-EPI formula was used to calculate the eGFR. Previous analyses have indicated that this formula works more optimally for capturing the later stages of declining CKD [5]. But the value of CKD-EPI formula for the primary aims of this analysis was that it

takes age, sex, and race into consideration, addressing the caveat above about potential bias if the conclusions were driven more by one subgroup of participants. Given our interest in the potential influence of obesity and central adiposity as an independent pathway of risk, we did not specifically correct for obesity when calculating the eGFR, even though it is possible that there is an influence of adiposity on muscle mass, which could have affected serum creatinine levels. It is also important to consider that the modeling assumed some causal directionality in the association between the identified risk factors and kidney function. In reality, the linkages with kidney health are more complex as exemplified by strong correlation between elevated BP and poor renal function. Future research should also include other measures of glomerular status, and employ some of the administered substances that provide a more specific indication of clearance rates in a clinical setting.

Conclusion

We demonstrated that a 5-class model of risk optimally captures the variations of comorbidity among prominent risk factors for CKD, resulting in a taxonomy comprised of Low Risk, Obese, Obese and Elevated BP, Non-Obese but Elevated BP, and High Risk. Membership in the High Risk class was associated with a higher probability of having lower kidney function (eGFR < 60 ml/min/1.73 m²). Conversely, the absence of the known risk factors can be considered protective and an indicative of a more robust kidney function even into older adulthood. The most novel aspect of this analysis was our confirmation that latent class membership of comorbidity of risk factors was associated with childhood SES, even after controlling for education level, current SES, age, gender, and race, documenting the importance of early rearing conditions for the potential development of CKD in adulthood. A clearer understanding of health disparities requires a consideration of both traditional clinical risk factors as well the pervasive influence of sociodemographic processes that can accelerate and worsen the physiological changes and dysregulation associated with normal aging.

Abbreviations

AIC: Akaike information criterion; *BIC*: Bayesian information criterion; *a-BIC*: sample size adjusted BIC; *BLRT* = bootstrapped likelihood ratio test; *BP*: blood pressure; *CI*: confidence interval; *CKD*: chronic

kidney disease; *CKD-EPI*: Chronic Kidney Disease Epidemiology Collaboration; *CRP* = C-reactive protein; *CRU*: clinical research unit; *DOHaD*: developmental origin of health and disease; *eGFR*: Estimated glomerular filtration rate; *IL-6* = interleukin-6; *IUGR*: intrauterine growth restriction; *LCA*: latent class analysis; *MIDUS*: Midlife in the United States; *MR*: mineralocorticoid receptor; *RAAS*: renin-angiotensin-aldosterone system; *SES*: socioeconomic status; *TGF*: tubuloglomerular feedback

Declarations

Ethics Approval and Consent to Participate

Ethics approval obtained from the institution review board from each institution involved in the MIDUS study, including University of Wisconsin-Madison, University of California, Los Angeles, and George Washington University. Written informed consent was obtained from the participants.

Consent for Publication

Not applicable.

Availability of Data and Materials

The MIDUS datasets used in this analysis are available in the Inter-university Consortium for Political and Social Research (ICPSR) website:

<https://www.icpsr.umich.edu/icpsrweb/ICPSR/series/00203/studies?archive=ICPSR&sortBy=7>

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

All authors read and approved the final manuscript. AS analyzed the data under supervision of BB. AS, JD, CC, and DM drafted the manuscript. DM and CC designed the study and directed implementation and data collection.

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Authors' Information

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Tables

Table 1

Descriptive Statistics for Class Indicators, Covariates, and Outcome ($N = 2,118$)

Variables	MIDUS 2 ($n = 1,255$)	MIDUS R ($n = 863$)	Overall ($N = 2,118$)
Risk Factors			
Elevated blood pressure (Systolic/diastolic $\geq 140/90$ or diagnosed by physician; %)	52.7	48.6	51.0
Insulin resistance (HbA1c $\geq 6.5\%$ or blood fasting glucose ≥ 126 mg/dL or diagnosed by physician; %)	20.1	17.4	19.0
Obese (BMI ≥ 30 Kg/m ² ; %)	41.2	45.2	42.8
Abdominally Obese (waist circumference ≥ 88 cm for women and ≥ 102 cm for men; %)	55.6	54.7	55.2
Hypercholesterolemic (total serum cholesterol ≥ 200 mg/dL or diagnosed by physician; %)	60.1	55.6*	58.3
Elevated IL6 (%)	32.2	24.8*	29.2
Elevated CRP (%)	31.2	24.7*	28.5
Sociodemographic Correlates			
Childhood SES			
Parental education less than HS/GED (%)	42.2	24.2*	34.9
Family of origin received welfare (%)	2.9	4.4*	3.5
Low subjective financial status (%)	27.4	33.6*	29.9
Mean total score of childhood SES (<i>SD</i> ; min-max)	3.80 (1.43; 0-6)	4.08 (1.46; 0-6)*	3.91 (1.45; 0-6)
Covariates			
Female (%)	56.8	52.1*	54.9
Mean age (<i>SD</i> ; min-max)	54.5 (11.7; 34-84)	50.8 (13.4; 25-76)*	53.0 (12.6; 25-84)
Non-Hispanic White (%)	77.2	68.6*	73.7
Education less than HS/GED (%)	27.9	17.3*	23.6
Mean total score adult SES (<i>SD</i> ; min-max)	4.73 (2.28; 0-8)	4.39 (2.38; 0-8)*	4.59 (2.33; 0-8)
Kidney Function (<i>M</i>, <i>SD</i>, range, %)			
Mean eGFR (<i>SD</i> , min-max)	90.4 (19.6; 3.7-150.7)	92.4 (18.5; 20.4-139.5)*	91.2 (19.2; 3.7-150.7)
eGFR < 60 ml/min/1.73 m ²	5.6	4.3	5.1
eGFR 60-89 ml/min/1.73 m ²	42.6	37.5	40.6
eGFR ≥ 90 ml/min/1.73 m ²	50.9	56.9	53.4

Note: MIDUS 2 = MIDUS wave 2, MIDUS R = MIDUS Refresher; *M* = mean, *SD* = standard deviation; * = significantly different from MIDUS 2 ($p < .05$)

Table 2

Model Fit Information for Latent Class Analysis

No. of classes	Log-likelihood	Degrees of freedom	AIC	BIC	CAIC	a-BIC	Entropy	BLRT
1	-9368.58	120	2252.38	2266.38	2305.99	2283.75		
2	-8475.15	112	495.52	580.39	595.39	532.74	.82	$p < .05$
3	-8391.03	104	343.28	473.42	496.42	400.34	.73	$p < .05$
4	-8335.72	96	248.66	424.07	455.07	325.58	.71	$p < .05$
5	-8306.75	88	206.72	427.39	466.39	303.48	.69	$p < .05$
6	-8289.67	80	188.57	454.50	501.50	305.18	.67	$p > .05$

Note: boldface type indicates selected model.

Table 3

Latent Class Membership and Item-Response Probabilities

Indicator	Class 1: Low Risk (36.40%)	Class 2: Obese (16.42%)	Class 3: Obese and Elevated BP (13.37%)	Class 4: Non-Obese but Elevated BP (14.95%)
Hypertensive	.28	.43	.70	.60
Insulin resistance	.07	.00	.28	.17
Large BMI	.02	.93	.68	.00
Abdominal obesity	.10	.93	.93	.37
Hypercholesterolemia	.47	.49	.78	.64
Elevated IL6	.07	.44	.00	.41
Elevated CRP	.02	.28	.00	.66

Note: boldface type indicates high probability.

Table 4

Childhood SES and probability of being in the non-healthy classes rather than the Low Risk

class ($N = 2,118$)

Predictors	Obese (16.42%)		Obese and Elevated BP (13.37%)		Latent C
	b (SE)	OR [95%CI]	b (SE)	OR [95%CI]	b (SE)
χ^2 ($df = 4$)					Non-Obese (14.95%)
Childhood SES (score)	15.28 **	0.09 (0.09)	1.09 [0.91-1.31]	-0.22 (0.07)	0.81 [0.70-0.93] *
Education (0 = no HS/GED; 1 = HS/GED or higher)	12.27 *	-0.67 (0.35)	0.51 [0.26-1.01]	-0.34 (0.30)	0.71 [0.44-1.27]
Adult SES (score)	72.69 ***	-0.16 (0.06)	0.86 [0.77-0.95] *	-0.23 (0.06)	0.79 [0.70-0.90] *
Age (years)	328.77 ***	-0.03 (0.02)	0.97 [0.94-1.00]	0.11 (0.02)	1.12 [1.00-1.16] *
Gender (0 = female, 1 = male)	50.73 ***	-0.62 (0.40)	0.54 [0.25-1.18]	1.09 (0.26)	2.98 [1.84-4.92] *
Race (0 = minorities, 1 = white)	22.07 ***	-0.59 (0.28)	1.82 [0.32-0.96] *	-0.15 (0.35)	0.86 [0.44-1.72]

Note: χ^2 = chi-square independence (*df* = degrees of freedom); the Low Risk was the reference class; *: $p < .05$; **: $p < .01$; ***: $p < .001$

Figures

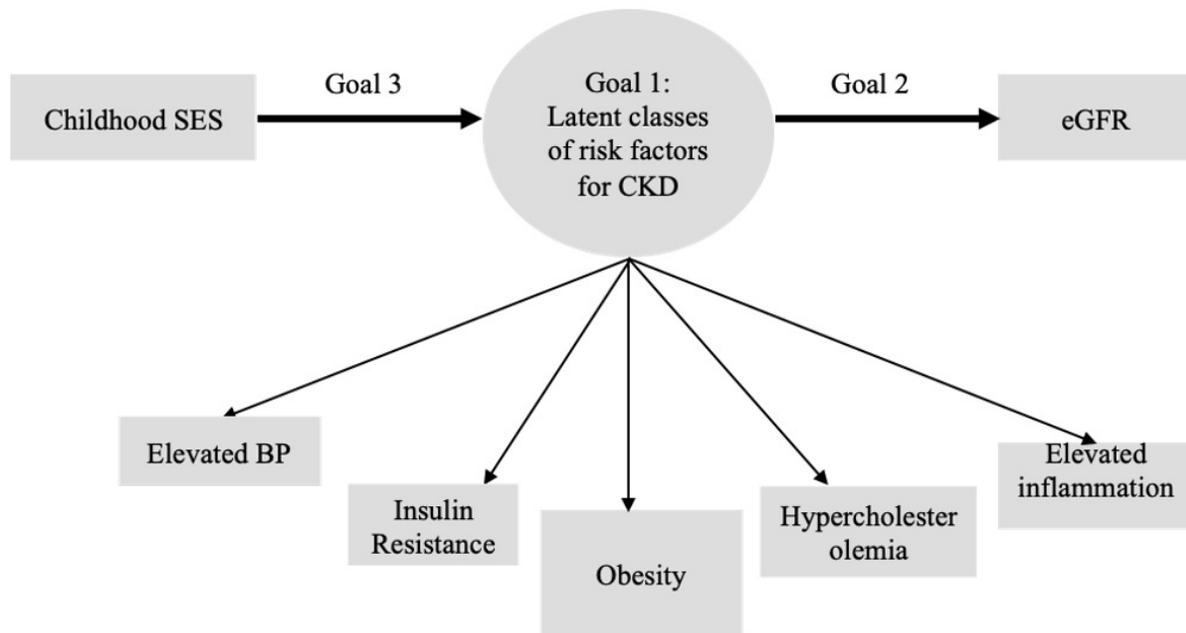


Figure 1

Visual representation of the hypothesis tested in this paper. First, we identified the heterogeneity of comorbidity in risk factors using latent class analysis (LCA). Second, we tested whether different characteristics of comorbidity in risk factors have different impact on kidney function. Third, we examined whether childhood SES, independent of education and adult SES, predicted latent classes of comorbidity in risk factors.

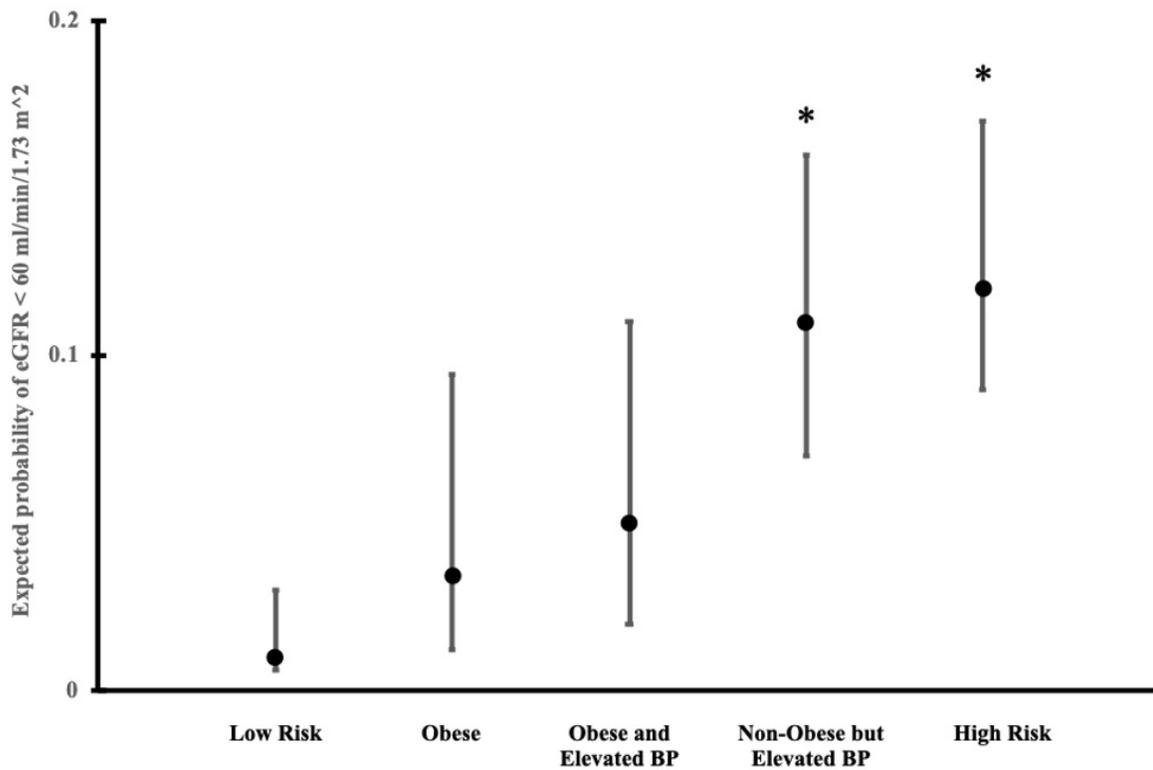


Figure 2

Expected probability with 95% CI for having eGFR < 60 ml/min/1.73 m² based on classes of CKD risk factors comorbidity; omnibus test: $\chi^2(4) = 23.66$, $p < .001$; *: significantly higher than the Low Risk class ($p < .05$; Bonferroni correction applied for multiple comparisons in pairwise comparison tests).