



Body Mass Index in Late Adolescence and Later Life Kidney Outcomes: A Population-Based Cohort Study in Swedish Men

Monika Vitkauskaitė, Ernesta Mačionienė, Rytis Stankevičius, Marius Miglinas, Joachim H. Ix, and Mattias Brunström

Rationale & Objective: The association between body mass index (BMI) and chronic kidney disease (CKD) is well established in middle-aged and older adults. Here, we assess the association of BMI in late adolescence with CKD, kidney failure, and acute kidney injury (AKI) later in life.

Study Design, Setting & Participants: Population-based cohort study including data from the Swedish Conscription Database, the National Patient Register, the Cause of Death Register, and Statistics Sweden. Conscripts with no history of diabetes, cardiovascular, kidney, or rheumatic diseases enlisted between 1969 and 1997 were followed until December 31, 2019.

Main Outcomes & Exposures: The study examined the impact of BMI on kidney outcomes. The primary outcome was incident chronic kidney disease. Secondary outcomes were stage 5 chronic kidney disease, end-stage kidney disease, and acute kidney injury.

Analytical Approach: Patients were stratified into the quintiles of BMI at conscription, and followed until events, death, or censoring, using Cox proportional hazards model, adjusted for baseline systolic and diastolic blood pressure, proteinuria, and socioeconomic factors.

Results: In total, 1,321,481 male participants with a mean age of 18.3 years and a mean BMI of 21.6 kg/m² were followed for an average of 35.6 years, generating a total of 47 million person-years of follow-up. During this period, the incidence of CKD-based on diagnosis codes was 5,590, whereas 2,357 subjects were diagnosed with end-stage kidney disease and 8,023 with AKI, respectively. The risk for CKD was increased for the fourth and fifth highest BMI quintile relative to the lowest (adjusted hazard ratio [aHR] 1.23; 95% confidence interval [CI], 1.13-1.35 for BMI 21.9-23.5 kg/m²; aHR 2.09; 95% CI, 1.93-2.26 for BMI >23.5 kg/m²). Patterns were similar for stage 5 CKD and end-stage kidney disease, whereas the risk for AKI was evident at the third and higher quintiles (aHR 1.14; 95% CI, 1.06-1.23 for BMI 20.7-21.9 kg/m²; aHR 1.31; 95% CI, 1.22-1.41 for BMI 21.9-23.5 kg/m²; and aHR 1.92; 1.79-2.05 for BMI ≥23.5 kg/m²).

Limitations: A retrospective observational study of male Swedish adolescents.

Conclusions: The findings of this study indicate that, for prevention of kidney disease, the optimal BMI in adolescence with reference to kidney outcomes is likely in the low-normal range.

Complete author and article information provided before references.

Correspondence to M. Vitkauskaitė (vitkausk.monika@gmail.com)

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Chronic kidney disease (CKD) and obesity are growing public health problems globally and are linked with one another, and obesity is modifiable.^{1,2} Since 1980, the average body mass index (BMI) has increased by 0.5 kg/m² per decade worldwide.³ The number of persons with CKD was 697.5 million in 2017, and the global prevalence of CKD has increased by 29.3% since 1990.⁴

Obesity can be linked to the development and progression of CKD through increasing risk for type 2 diabetes (T2D) and hypertension.⁵ However, most studies investigating the association between BMI and kidney outcomes have evaluated middle-aged and older adults. Thus, optimal BMI targets to prevent CKD in earlier life are unknown.

Previous studies in adolescents have found an association between BMI and kidney function, suggesting that puberty may be a critical window for future kidney health.⁶ This may be related to an imbalance between nephron mass and increasing body size, rapid sex hormone-driven metabolic changes, an increased cumulative effect of years at higher BMI with the condition starting in early life, or a combination of these factors.^{7,8}

As large longitudinal studies with long-term follow-up assessing the association between BMI in adolescence and progression to CKD, kidney failure, and acute kidney injury (AKI) are lacking, the aim of this study was to investigate the association of BMI in late adolescence with incident CKD, kidney failure, and AKI later in life.

METHODS

We included data from the Swedish Conscription Database, the Swedish National Patient Register (NPR), the Swedish Cause of Death Register (CDR), and Statistics Sweden, linked through the unique personal identification number given to all Swedish residents. Ethical approval was granted by the Swedish Ethical Review Authority, Dnr-2020-04149 with amendment Dnr 2022-00514-02.

Study Population

Military conscription was mandatory by law for all male Swedish citizens during the inclusion period of this study, from 1969 to 1997. From 1980 onward, women could

PLAIN LANGUAGE SUMMARY

This study investigates the long-term link between body mass index (BMI) during late adolescence and kidney failure and acute kidney injury. It draws from a large, population-based Swedish cohort, tracking over a million young men over decades. The research shows that higher BMI in adolescence is associated with an increased risk of kidney problems as adults, with those in the higher BMI ranges facing a significantly greater chance of developing chronic kidney disease and acute kidney injury. The risk was particularly high for individuals with higher BMI levels. These findings suggest that maintaining a low-normal BMI during adolescence may help prevent kidney-related diseases later in life.

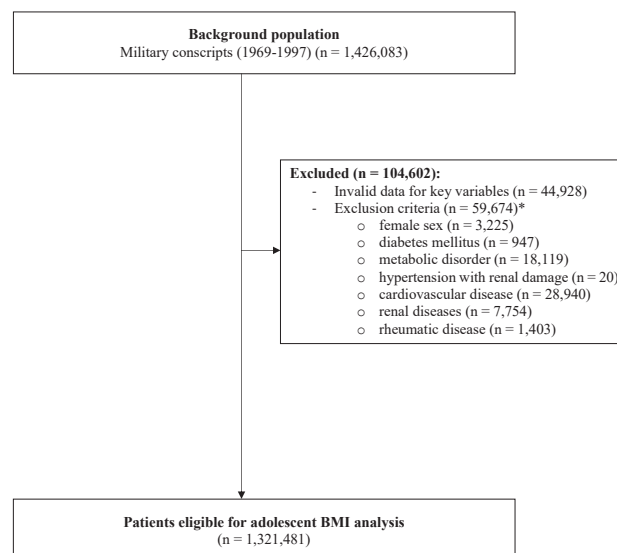
volunteer for military service, but participation rates were low during the study period. All conscripts underwent a medical assessment to deem their fitness for military service, including an assessment of BMI.

Because of the very low number of females in the conscription dataset, they were excluded from the study. Other exclusion criteria for this study included a diagnosis of diabetes mellitus (ICD-9 code 250), metabolic disorders (ICD-9 codes 270-279), hypertension with kidney damage (ICD-9 codes 400.30, 403.99, and 404.99), cardiovascular disease except hypertension and venous thromboembolism (ICD-9 codes 390-399, and 406-449), kidney diseases (ICD-9 codes 580-593), and rheumatic disease (ICD-9 codes 712-714) at the time of conscription. Diagnosis codes were recorded by the attending physician during the medical examination, and no additional data to support the codes are available (Fig 1).

Baseline Data

The BMI was defined as weight (in kilograms) divided by height (in meters) squared. Height and weight were measured in light clothing without shoes. Resting systolic and diastolic blood pressure were measured in a supine position with an appropriately sized cuff at heart level and after 5-10 minutes of rest. A single measurement was made if BP was 145/50-85 mm Hg or less. If BP was outside these limits, a second measurement was made and entered into the database. The BP was measured by auscultatory method by trained nurses or physicians.⁹ Urine dipstick tests were used to assess proteinuria, categorized as negative, trace, or positive.

Socioeconomic data, including educational level, income, and civil status, were collected from Statistics Sweden at the age of 40 years for all participants. We chose age 40 years because most people have attained their maximum educational level and a representative income by that age. Educational level was classified as compulsory, secondary, or university degree. For income, we calculated deciles for each year to account for inflation. Civil status



* the number of participants meeting any exclusion criteria is smaller than the sum of the number of participants meeting each criterion because some participants had several diagnoses leading to exclusion.

Figure 1. Flow chart of the patients included in the study.

was categorized as married, unmarried, divorced, or widowed.

Follow-Up and Outcome Parameters

Data on kidney disease were collected from the Swedish NPR and CDR. The NPR includes all ICD codes for all hospitalizations in Sweden since 1987, with full coverage for the most populous regions already from the early 1970s. The CDR includes all main and contributing causes of death with full coverage since 1961.

The primary endpoint was incident CKD, defined as ICD10 codes N18.3 to N18.9 or ICD9 code 585 in either register. Secondary endpoints were stage 5 CKD (ICD10 code N18.5), kidney failure (ICD10 codes N18.5; Z94.0), and AKI (ICD10 code N17 or ICD9 code 584). The specificity for CKD diagnosis in the NPR has previously been estimated to 94%.¹⁰

Statistical Analysis

Participants were stratified into the quintiles of BMI at conscription as the primary exposure variable. We chose quintiles instead of clinically established BMI categories (such as overweight and obesity) because the vast majority of included individuals were normal-weight, and we wanted to assess potential differences even within the normal BMI range. Because of the large sample size, quintiles were separated at the second to fourth decimal, resulting in the same rounded value appearing in multiple categories.

We performed time-to-event analysis to assess the association between BMI category and kidney outcomes. End

of the follow-up was December 31, 2019. Follow-up time was calculated from the date of conscription until the kidney event (depending on which outcome was analyzed), death, or censoring, whichever came first.

We first performed Kaplan-Meier analysis and log-log plots to assess the survival function and the proportional hazards assumption between exposure groups. We then performed Cox proportional hazards modeling to assess the association between exposure and outcome, adjusted for covariates systolic and diastolic blood pressure, and proteinuria at conscription, and income, educational level, and civil status at 40 years of age. Hazard ratios (HRs) with 95% CIs were calculated for each BMI quintile, setting the lowest as a reference.

Because diabetic kidney disease is the most common cause of CKD,¹¹ and as a higher BMI is the dominant risk factor for T2D, the effect of BMI on CKD is likely frequently mediated through diabetes. To explore the association between BMI and CKD, independent of diabetes, we performed a sensitivity analysis, removing all participants diagnosed with diabetes during follow-up.

Statistical analysis was performed with StataMP v 16.1.

RESULTS

There were 1,321,481 Swedish conscripts that met the inclusion criteria for this study. The mean±SD age was 18.3±0.8 years and the mean BMI was 21.6±2.6 kg/m² at baseline (Table 1).

During an average follow-up of 35.6±8.6 years, generating more than 47 million person-years of exposure time, 5,590 subjects developed CKD, 1,923 developed CKD stage 5, 2,357 developed kidney failure, and 8,023 developed AKI. Kaplan-Meier curves for each outcome, stratified by BMI quintile at conscription, are shown in Figure 2. Cox regression analyses found progressively higher risk for CKD, CKD stage 5, and kidney failure from the fourth quintile (BMI ≥21.9 kg/m²), whereas the risk for AKI increased already from the third quintile (BMI ≥20.7 kg/m²) when compared with the lowest BMI category (Table 2). Results were virtually unchanged by adjustment for covariates.

In sensitivity analyses, exploring the impact of T2D on incident CKD, we found that 1,380 out of 5,593 CKD cases had a diabetes diagnosis before CKD diagnosis or censoring. Removing these participants from the analysis attenuated the association between the highest BMI category and CKD slightly; however, the risk for CKD remained statistically significantly elevated at the four and fifth quintile (BMI ≥21.9 kg/m²) (Table 3).

DISCUSSION

Few studies have examined the association between adolescent BMI and the subsequent CKD. In this population-based cohort study with more than 47 million person-years of follow-up, higher BMI values in late adolescence were associated with increased risk of CKD, stage 5 CKD, kidney failure, and AKI. Of importance, this

Table 1. Characteristics of Study Subjects at Baseline

Variable	Valid Data	BMI Quintile 1 (n = 265,965)		BMI Quintile 2 (n = 264,516)		BMI Quintile 3 (n = 265,276)		BMI Quintile 4 (n = 263,019)		BMI Quintile 5 (n = 262,705)	
		Mean/No.	SD/%	Mean/No.	SD/%	Mean/No.	SD/%	Mean/No.	SD/%	Mean/No.	SD/%
Age	1,321,481	18.3	0.7	18.3	0.7	18.3	0.7	18.3	0.8	18.4	1.0
Height	1,321,481	179.2	6.7	179.3	6.5	179.1	6.5	179.0	6.5	178.8	6.6
Weight	1,321,481	59.4	5.1	64.8	4.8	68.4	5.0	72.6	5.4	82.0	9.1
BMI	1,321,481	18.5	0.8	20.1	0.3	21.3	0.3	22.6	0.5	25.6	2.1
SBP	1,321,481	126.1	10.8	127.3	10.7	128.2	10.7	129.2	10.7	131.0	10.9
DBP	1,321,481	67.2	9.7	67.0	9.8	67.1	9.9	67.2	10.0	68.0	10.3
Proteinuria	1,297,823										
Negative		258,878	98.9	258,175	99.2	258,948	99.3	256,633	99.4	255,359	99.42
Trace		274	0.1	145	0.1	109	0.1	75	0.03	56	0.02
Positive		2,630	1.0	1,997	0.7	1,640	0.6	1,482	0.57	1,422	0.56
Educational level ^a	1,264,161										
Compulsory		40,391	15.9	34,699	13.7	32,201	12.7	32,150	12.8	37,922	15.1
Secondary		130,519	51.2	127,114	50.2	127,781	50.5	127,990	50.9	140,743	56.0
University		83,806	32.9	91,201	36.1	93,614	36.8	91,237	36.3	72,802	28.9
Civil status ^a	1,265,899										
Unmarried		119,245	46.8	108,302	42.8	104,654	41.2	103,151	41.0	112,140	44.5
Married		115,665	45.3	124,625	49.2	128,900	50.8	128,018	50.9	118,487	47.1
Divorced		19,849	7.8	20,100	7.9	20,025	7.9	20,207	8.0	20,856	8.3
Widowed		362	0.1	330	0.1	326	0.1	318	0.1	339	0.1

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; No, number; SBP, systolic blood pressure; SD, standard deviation.

^aAt 40 years of age.

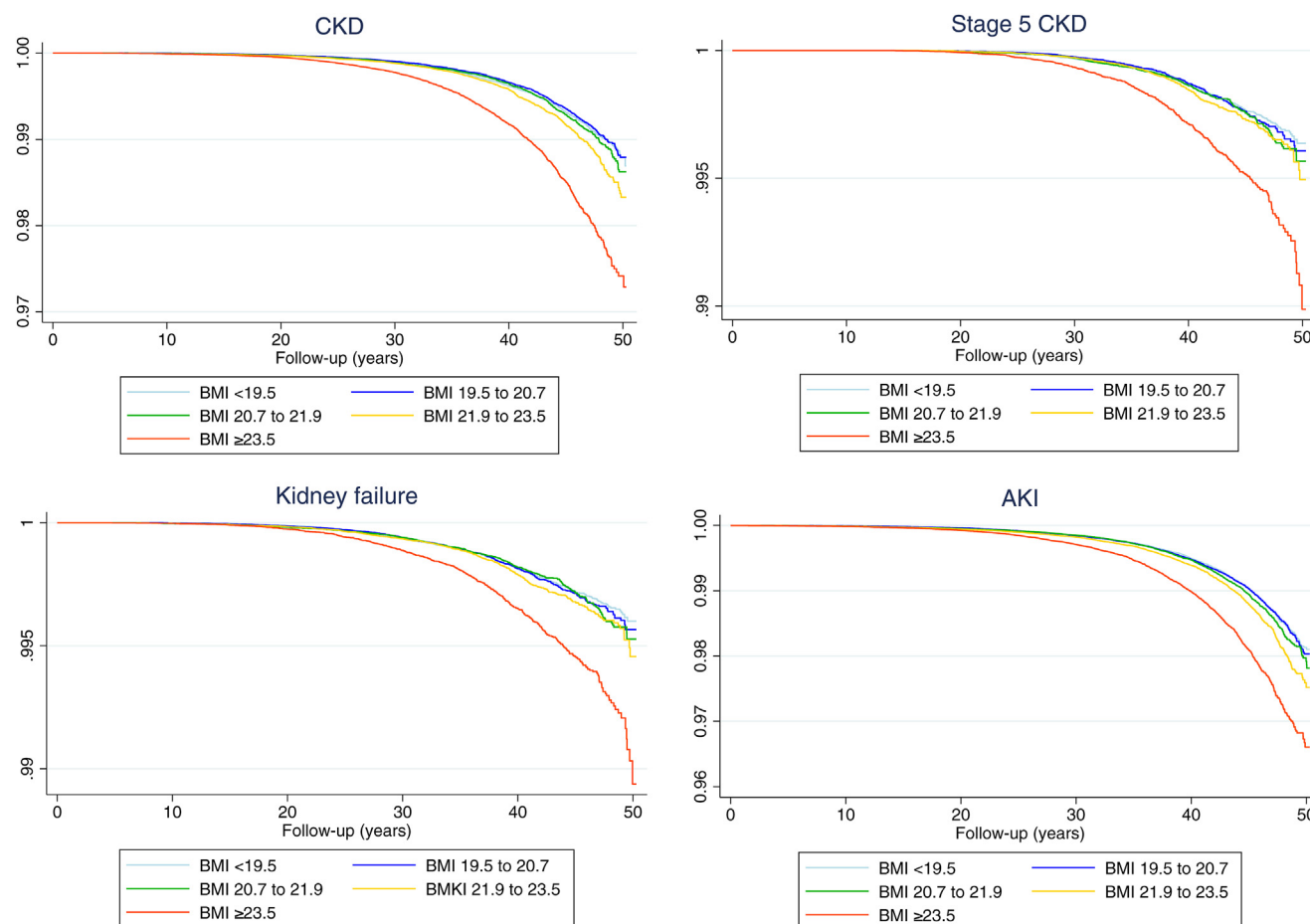


Figure 2. Kaplan-Meier estimates for the association between BMI in late adolescence and kidney outcomes. BMI, body mass index.

association was evident already from BMI levels that are considered normal, indicating that for kidney health, the optimal BMI in adolescence may be in the lower range of the normal spectrum.

Some studies only provided associations with kidney failure, leaving the association between BMI and more common but less severe forms of CKD less studied.^{12–14} A recent Mendelian randomization study pointed toward a causal effect of obesity on incident CKD by using the genetic variants as instrumental variables.⁵ This is supported by our findings from an adolescent population, free of important comorbid conditions and therefore less prone to confounding.

Obesity increases the risk for diabetes and hypertension, the 2 most common causes of kidney failure.¹⁵ Thus, a mediatory pathway between BMI and CKD, through T2D and hypertension is very likely. Of importance, we found that higher BMI values in late adolescence were associated with CKD, stage 5 CKD, kidney failure, and AKI, after adjustment for systolic and diastolic blood pressure, and when T2D was accounted for in sensitivity analyzes, indicating an additional independent effect.

The driving factor linking obesity to CKD remains to be explained. However, neuroendocrine mechanisms, such as

insulin resistance, stimulation of the renin-angiotensin-aldosterone system, sympathetic nervous system activation, and adipose-renal hormonal axis disturbances, are likely to play significant roles.^{16–20} Higher BMI is associated with kidney sinus fat and ectopic lipid accumulation, glomerular hyperfiltration, and hypertension that ultimately culminate in glomerulomegaly and focal or segmental glomerulosclerosis, all of which are linked to an increased risk of CKD and consequently kidney failure.^{21–24} The typical obesity-associated glomerular disorder is characterized by glomerulomegaly with vascular dilatation and mesangial expansion. In addition, to these findings, mild tubular atrophy, interstitial fibrosis, podocyte hypertrophy, and reduced capillary density are also noted.^{25,26} Glomerular hyperfiltration, a disturbed transrenal pressure gradient due to hypervolemia and cardiac changes associated with obesity, may predispose to AKI in overweight subjects.^{27–29}

A critical issue is to differentiate the accumulation of risk due to lifelong overweight or obesity exposure⁶ compared with sensitive periods across the life span, such as adolescence.⁸ Interestingly, we found an association of BMI in adolescence with future CKD, starting from a BMI of 21.9 kg/m² or greater, thus extending previous

Table 2. Kidney Outcomes According to Late Adolescent BMI Quintiles

Outcome	BMI at Conscription (Quintiles)	Events/ Participants	Unadjusted HR (95% CI)	Adjusted HR ^a (95% CI)
Primary outcome				
CKD	< 19.5	1,078/265,965	1.00 (ref)	1.00 (ref)
	19.5-20.7	910/264,516	0.94 (0.86-1.03)	0.98 (0.89-1.07)
	20.7-21.9	939/265,276	1.03 (0.94-1.13)	1.06 (0.97-1.16)
	21.9-23.5	1,018/263,019	1.21 (1.11-1.32)	1.23 (1.13-1.35)
	>23.5	1,645/262,705	2.22 (2.06-2.40)	2.09 (1.93-2.26)
Secondary outcomes				
CKD stage 5	< 19.5	344/265,965	1.00 (ref)	1.00 (ref)
	19.5-20.7	315/264,516	1.02 (0.87-1.19)	1.04 (0.89-1.22)
	20.7-21.9	319/265,276	1.10 (0.94-1.28)	1.10 (0.94-1.28)
	21.9-23.5	422/263,019	1.16 (1.00-1.35)	1.15 (0.99-1.35)
	>23.5	523/262,705	2.22 (1.94-2.55)	2.04 (1.77-2.34)
Kidney Failure	<19.5	450/265,965	1.00 (ref)	1.00 (ref)
	19.5-20.7	427/264,516	1.04 (0.91-1.18)	1.06 (0.93-1.21)
	20.7-21.9	408/265,276	1.04 (0.91-1.19)	1.05 (0.92-1.20)
	21.9-23.5	422/263,019	1.15 (1.01-1.32)	1.15 (1.01-1.32)
	>23.5	650/262,705	1.97 (1.75-2.22)	1.78 (1.57-2.01)
AKI	< 19.5	1,572/265,965	1.00 (ref)	1.00 (ref)
	19.5-20.7	1,429/264,516	1.01 (0.94-1.09)	1.06 (0.99-1.14)
	20.7-21.9	1,422/265,276	1.08 (1.00-1.16)	1.14 (1.06-1.23)
	21.9-23.5	1,515/263,019	1.24 (1.16-1.34)	1.31 (1.22-1.41)
	>23.5	2,085/262,705	1.95 (1.82-2.08)	1.92 (1.79-2.05)

Abbreviations: AKI, acute kidney injury; BMI, body mass index; CKD, chronic kidney disease; CKD stage 5, chronic kidney disease stage 5; HR, hazard ratio; ref, reference; 95% CI, 95 % confidence interval.

^aAdjusted for systolic and diastolic blood pressure, proteinuria, and income, educational level and civil status at age 40 years.

knowledge into the non-overweight range of BMI. This suggests a dose-effect of BMI on the CKD development and further supports that adolescence may be a critical window for the future kidney health. This lends additional support from the Medical Research Council National Survey of Health and Development study, which found that overweight children and young adults were 1.27-2.04-fold more likely to get CKD when compared with normal-weight peers.³⁰ Furthermore, early life increase in BMI was associated with kidney failure risk later in life, and few longitudinal studies show that the risk for kidney failure and CKD increases with higher BMI.^{12,13,30-33}

The association between BMI and incidence of AKI is less well described; however, there are studies showing an association between high BMI and higher incidence of AKI in ICU patients after severe trauma or when critically ill.^{34,35} Our findings extend previous knowledge to the general

population. There are 3 main mechanisms which could potentially explain the relationship between high BMI and AKI development.³⁵ First, impaired natriuresis activates the renin-angiotensin system, causing hemodynamic changes in the glomerulus (hyperperfusion and hyperfiltration).^{23,36} Second, in obesity adipocytes secrete proinflammatory cytokines, such as TNF- α and IL-6, and prompt an intracellular oxidative stress.³⁷ Third, obesity is linked to an increased hemodynamic and metabolic load on each glomerulus, resulting in a low number of functional nephrons.^{35,38}

Strengths of this study include its assessment of nearly all men in Sweden, long-term follow-up, and uniform assessment of outcomes. This study also has important limitations. First, the BMI does not allow to estimate body composition, and elevated BMI due to higher-than-average muscle mass may affect kidney outcomes differently when compared with excess adipose tissue. Indeed, a previous

Table 3. Cox Proportional Hazard Regression for CKD After Removing all Subjects With Type 2 Diabetes Diagnosis Before CKD Event or Censoring

Outcome	BMI at Conscription (Quintiles)	Events/Participants	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
CKD	<19.5	884/260,082	1.00 (ref)	1.00 (ref)
	19.5-20.7	749/258,873	0.94 (0.85-1.03)	0.97 (0.88-1.07)
	20.7-21.9	750/259,336	1.00 (0.90-1.10)	1.02 (0.92-1.13)
	21.9-23.5	769/255,977	1.11 (1.01-1.22)	1.13 (1.03-1.25)
	>23.5	1,058/249,272	1.79 (1.63-1.95)	1.70 (1.55-1.86)

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; HR, hazard ratio; 95% CI, 95 % confidence interval.

study found that increased muscle-to-fat ratio was associated with lower risk to develop CKD (aHR, 0.83; 95% CI, 0.70-0.98).³⁹ Second, our cohort consisted of men, due to conscription specifics, and results do not necessarily apply to females. Some studies report the link between obesity and kidney failure was only evident women.^{40,41} However, a prospective study from Japan showed a greater cumulative incidence of kidney failure in adults with a baseline BMI of 25.5 or greater when compared with adults with a baseline BMI of less than 21.0, and such an association was more prominent in men than in women. Therefore, additional studies are needed in adolescent women.⁴² Third, our study was retrospective in the sense that it relied on already collected data, which does not allow us to include all relevant baseline variables, most importantly baseline kidney function in adolescence. Fourth, all outcomes were collected through hospital-based ICD codes without access to laboratory tests and other diagnostic procedures. This likely leads to a substantial underestimation of the total number of CKD events, in particular moderate CKD, which is reflected by the low absolute numbers reported here compared with previous prevalence studies.^{43,44} Finally, this study evaluates only the Swedish population and has therefore limited applicability to other cultures and ethnicities.

To conclude, the BMI in late adolescence was associated with increased risk of CKD, stage 5 CKD, kidney failure, and AKI during an average of 35 years of follow-up. These associations were evident even within the normal range of BMI, indicating that the optimal BMI in male adolescents with reference to kidney outcomes is likely in the low-normal range.

ARTICLE INFORMATION

Authors' Full Names and Academic Degrees: Monika Vitkauskaitė, MD, Ernesta Mačionienė, MD, Rytis Stankevičius, MD, Marius Miglinas, Joachim H. Ix, and Mattias Brunström

Authors' Affiliations: Vilnius University, Vilnius, Lithuania (MV, EM, RS, MM); Clinic of Gastroenterology, Nephro-Urology and Surgery, Institute of Clinical Medicine, Vilnius University, Vilnius, Lithuania (EM, MM); Division of Nephrology-Hypertension, Department of Medicine, University of California San Diego, and Veterans Affairs San Diego Healthcare System, San Diego, California (JHI); and Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden (MB).

Address for Correspondence: Monika Vitkauskaitė, MD, Vilnius University, Santariskiu Street 2, Vilnius LT-08410, Lithuania. Email: vitkausk.monika@gmail.com

Authors' Contributions: MB had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; concept and design: MM, MB; acquisition, analysis, or interpretation of data: all authors; statistical analysis: MB; administrative, technical, or material support: all authors; supervision: MB, JHI, MM. Each author contributed important intellectual content during article drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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