

## Mid-Adulthood Risk Factor Profiles for CKD

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### ABSTRACT

Early identification of CKD risk factors may allow risk factor modification and prevention of CKD progression. We investigated the hypothesis that risk factors are present  $\geq 30$  years before the diagnosis of CKD in a case-control study using data from the Framingham Offspring Study. Patients with incident CKD (eGFR  $\leq 60$  ml/min per 1.73 m<sup>2</sup>) at examination cycles 6, 7, and 8 were age- and sex-matched 1:2 to patients without CKD at baseline (examination 5). CKD risk factors were measured at each examination cycle. Logistic regression models, adjusted for age, sex, and time period, were constructed to compare risk factor profiles at each time point between cases and controls. During follow-up, 441 new cases of CKD were identified and matched to 882 controls (mean age 69.2 years, 52.4% women). Those who ultimately developed CKD were more likely to have hypertension (odds ratio [OR], 1.76; 95% confidence interval [CI], 1.23 to 2.51), obesity (OR, 1.71; 95% CI, 1.14 to 2.59), and higher triglyceride levels (OR, 1.43; 95% CI, 1.12 to 1.83) 30 years before CKD diagnosis, and were more likely to have hypertension (OR, 1.38; 95% CI, 1.07 to 1.79), higher triglyceride levels (OR, 1.35; 95% CI, 1.11 to 1.64), lower HDL<sub>c</sub> (OR, 0.89; 95% CI, 0.81 to 0.97), and diabetes (OR, 2.90; 95% CI, 1.59 to 5.29) 20 years before CKD diagnosis. These findings demonstrate that risk factors for CKD are identifiable  $\geq 30$  years before diagnosis and suggest the importance of early risk factor identification in patients at risk for CKD.

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CKD is a major public health problem that affects approximately 10%–15% of adults in the United States.<sup>1,2</sup> Even small decreases in GFR are associated with a significant reduction in life expectancy.<sup>3</sup> CKD is also recognized as an independent risk factor for cardiovascular disease.<sup>4</sup> The risk of cardiovascular disease increases at more advanced stages of CKD, particularly in those patients with proteinuria.<sup>4</sup>

CKD is commonly asymptomatic early in the course of the disease and, as a result, awareness of CKD among the general population remains low.<sup>5</sup> Risk factors for CKD identified in prospective studies include age, hypertension, ethnicity, diabetes, smoking, low HDL cholesterol (HDL<sub>c</sub>), proteinuria, and obesity.<sup>6–8</sup> However, the majority of studies have evaluated risk factors at, or near, the time of diagnosis of CKD when risk factor modification may be too late to prevent progression. It is likely that CKD risk factors are elevated decades before the diagnosis of CKD. If shown to be true, early identification of risk factors in young to mid-adulthood could have important

consequences for the timing of screening and treatment for CKD risk factors. Thus, the goal of our study was to evaluate the long-term risk factor burden borne by patients up to 30 years before the diagnosis of CKD.

### RESULTS

#### Study Sample Characteristics

Table 1 shows the risk factor profiles of the cases and controls at each time point. The mean age at the

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**Table 1.** Comparison of risk factors between CKD cases and controls in the Framingham Heart Study over time

Risk Factor	Timing of Risk Factor Measurement											
	At Time of CKD Diagnosis		10 yr before CKD Diagnosis		20 yr before CKD Diagnosis		30 yr before CKD Diagnosis					
	Controls (n=882)	Cases (n=441)	Controls (n=880)	Cases (n=441)	Controls (n=866)	Cases (n=433)	Controls (n=519)	Cases (n=262)				
Continuous characteristics, mean (SD)												
Age (yr)	69.2 (7.9)	69.4 (7.9)	59.0 (8.1)	59.2 (8.1)	48.4 (8.6)	48.7 (8.4)	41.1 (7.7)	41.1 (7.8)				
Calendar year of examination visit	2001 (4)	2001 (4)	1990 (5)	1991 (5)	1980 (5.7)	1980 (5)	1974 (2)	1974 (2)				
Systolic BP (mmHg)	134 (19)	134 (21)	131 (18)	135 (20)	125 (16.3)	127 (17)	121 (15)	126 (16)				
Diastolic BP (mmHg)	73 (10)	72 (11)	79 (10)	80 (10)	80 (10)	81 (9)	79 (9)	82 (11)				
LDL cholesterol (mg/dl)	116 (35)	113 (37)	135 (35)	135 (36)	136 (34)	136 (36)	129 (34)	131 (37)				
HDL cholesterol (mg/dl)	54 (17)	51 (16)	51 (15)	49 (15)	52 (15)	50 (15)	52 (15)	51 (15)				
Log triglycerides (mg/dl)	4.8 (0.5)	4.8 (0.5)	4.7 (0.6)	4.8 (0.6)	4.5 (0.6)	4.6 (0.7)	4.3 (0.6)	4.5 (0.7)				
BMI (kg/m <sup>2</sup> )	27.8 (4.8)	28.6 (5.2)	27.2 (4.5)	27.7 (4.8)	26.2 (4.1)	26.6 (4.4)	25.6 (3.8)	26.2 (4.2)				
Continuous characteristics, median (25th percentile, 75th percentile)												
eGFR (ml/min per 1.73 m <sup>2</sup> ) <sup>a</sup>	78.4 (69.3, 88.2)	54.2 (48.0, 57.8)	84.9 (75.2, 93.8)	80.5 (70.3, 88.9)	89 (60, 133)	97 (64, 156)	74 (48, 112)	85 (53, 141)				
Triglycerides (mg/dl)	115 (82, 165)	120 (89, 165)	114 (76, 153)	117 (84, 177)	89 (60, 133)	97 (64, 156)	74 (48, 112)	85 (53, 141)				
Categorical characteristics, n (%)												
Women	462 (52.4)	231 (52.4)	462 (52.5)	231 (52.4)	453 (52.3)	226 (52.2)	266 (51.3)	136 (51.9)				
Decade of examination visit												
2000–2008	419 (47.5)	198 (44.9)	1 (0.1)	3 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)				
1990–1999	463 (52.5)	243 (55.1)	415 (47.2)	212 (48.1)	10 (1.2)	2 (0.5)	0 (0.0)	0 (0.0)				
1980–1989	0 (0.0)	0 (0.0)	464 (52.7)	226 (51.3)	523 (60.4)	266 (61.4)	41 (7.9)	19 (7.3)				
1970–1979	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	333 (38.5)	165 (38.1)	478 (92.1)	243 (92.8)				
Hypertension	544 (61.7)	312 (70.8)	394 (44.9)	249 (56.5)	247 (28.6)	153 (35.4)	97 (18.8)	75 (28.7)				
Proteinuria	115 (21.1)	73 (26.7)	134 (16.0)	78 (18.5)	29 (5.7)	20 (7.9)	5 (1.0)	4 (1.6)				
Diabetes	158 (17.9)	108 (24.6)	79 (9.2)	61 (14.5)	19 (2.3)	27 (6.5)	17 (3.3)	15 (5.8)				
Hypertension treatment	412 (46.7)	277 (62.8)	227 (25.9)	165 (37.4)	75 (8.7)	59 (13.7)	62 (12.0)	49 (18.7)				
BMI ≥30 kg/m <sup>2</sup>	249 (28.2)	152 (34.5)	211 (24.0)	121 (27.4)	141 (16.3)	83 (19.2)	178 (34.4)	101 (38.7)				
Current smoker	75 (8.5)	32 (7.3)	156 (17.8)	80 (18.2)	253 (29.3)	129 (29.9)	178 (34.4)	101 (38.7)				

<sup>a</sup>The sample size for eGFR measurement is 177 cases and 349 controls for 10 years before diagnosis.

<sup>b</sup>Too few to report.

<sup>c</sup>Measurement not available.

time of CKD diagnosis was 69.2 years and 52.4% of participants were women. The median eGFR at the time of CKD diagnosis was 54.2 ml/min per 1.73 m<sup>2</sup> (IQR, 48.0–57.8 ml/min per 1.73 m<sup>2</sup>). The majority of participants (52.5%) were diagnosed with CKD between 1990 and 1999, whereas the remaining cases were diagnosed after 2000. At the time of diagnosis, participants were more likely to have hypertension (70.8% versus 61.7%;  $P=0.001$ ) and diabetes (24.6% versus 17.9%;  $P=0.01$ ). Cases also had higher triglycerides and lower HDL<sub>c</sub> and were more likely to be receiving treatment for hyperlipidemia. Obesity was more prevalent among cases as was the presence of dipstick proteinuria. Figure 1 shows the comparison of mean systolic and diastolic BP and the proportion of participants with hypertension at each time point from 30 years before the time of CKD diagnosis. Figure 2 shows the comparison of mean log triglycerides, mean HDL<sub>c</sub>, and the proportion of participants with diabetes at each time point. Figure 3 graphically displays the comparison of mean body mass index (BMI) and the proportion of participants with obesity over the course of the study.

### Risk Factors 30 Years before CKD Diagnosis

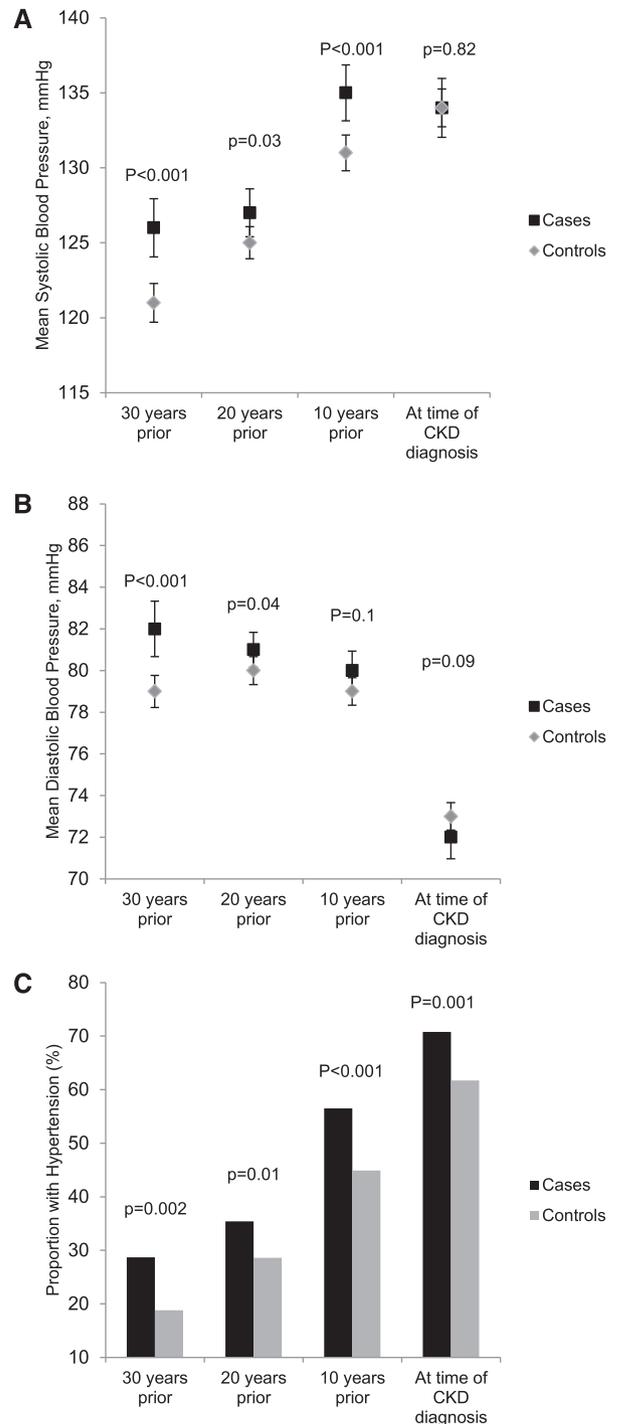
Table 2 shows age- and sex-adjusted odds ratios (ORs) of CKD for each risk factor. Differences in risk factors among those destined to develop CKD were present as much as 30 years before diagnosis. Increasing systolic BP and diastolic BP were associated with a higher future risk of CKD (OR, 1.22; 95% confidence interval [95% CI], 1.10 to 1.35; and OR, 1.18; 95% CI, 1.09 to 1.28 per 10-mmHg increment, respectively). The presence of hypertension in middle age resulted in a near doubling of CKD risk (OR, 1.76; 95% CI, 1.23 to 2.51). There was no association between HDL<sub>c</sub> or LDL levels and CKD 30 years before diagnosis, although increased serum triglycerides were associated with future CKD. Participants with obesity 30 years before diagnosis had a significantly increased risk of future CKD (OR, 1.71; 95% CI, 1.14 to 2.59) compared with participants without obesity.

### Risk Factors 20 Years before CKD Diagnosis

A similar pattern of risk factors was apparent 20 years before CKD diagnosis. Systolic BP, diastolic BP, and hypertension were associated with future CKD. Participants who developed CKD were more likely to have low HDL<sub>c</sub> and elevated triglycerides. Diabetes was nearly three times more likely to be present in participants who developed CKD 20 years before diagnosis (OR, 2.90; 95% CI, 1.59 to 5.29). There was a trend toward higher BMI in those who developed CKD (OR, 1.15; 95% CI, 0.99 to 1.32 per 5-kg/m<sup>2</sup> increase in BMI).

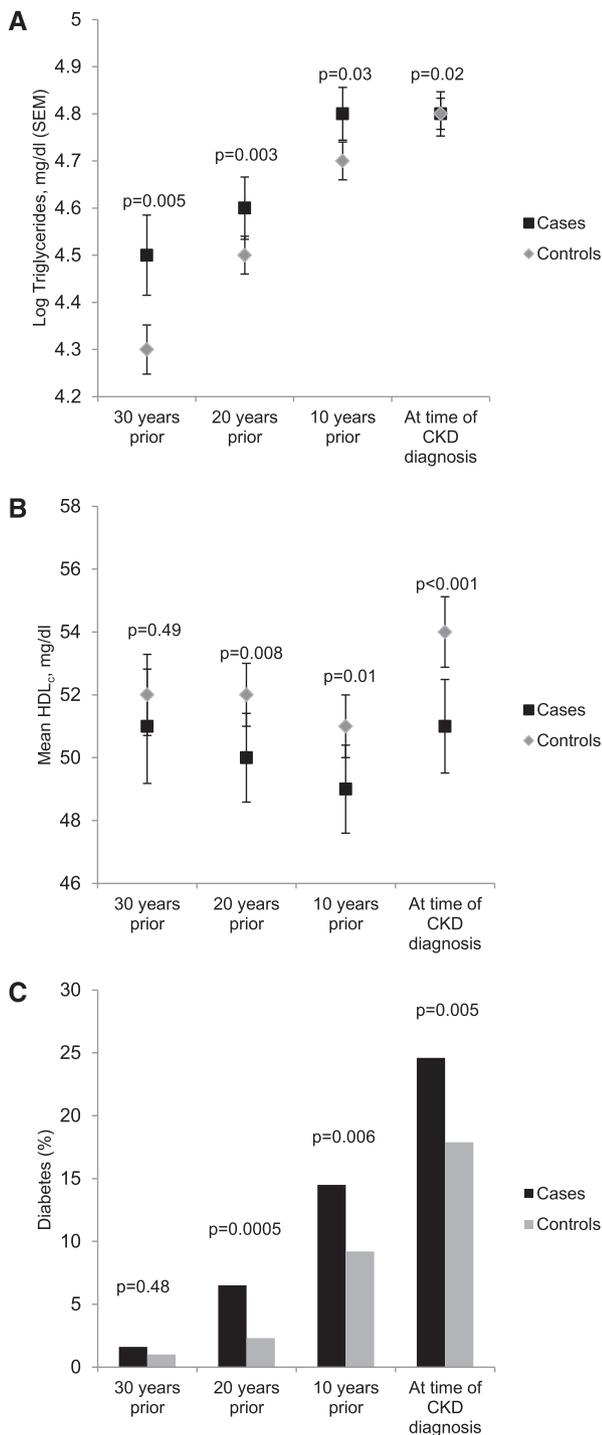
### Risk Factors 10 Years before CKD Diagnosis

Up to 10 years before CKD diagnosis, the presence of hypertension and dyslipidemia (elevated triglycerides and decreased HDL<sub>c</sub>) was associated with future CKD. Not unexpectedly, there was a higher risk of diabetes in those



**Figure 1.** Differences in blood pressure and hypertension in cases and controls up to 30 years before CKD diagnosis. Comparison of the mean systolic BP (A), diastolic BP (B), and proportion of participants with hypertension (C) in cases and controls at the time of CKD diagnosis and at time points 10, 20, and 30 years before diagnosis. The  $P$  values and SEM bars are derived from the logistic regression model.

individuals who later developed CKD (OR, 1.66; 95% CI, 1.16 to 2.38) although the association was attenuated relative to earlier time points.



**Figure 2.** Risk factor profiles in cases and controls up to 30 years prior to CKD diagnosis. Comparison of the log triglycerides (A), mean HDL<sub>c</sub> (B), and proportion of participants with diabetes (C) in cases and controls at the time of CKD diagnosis and at time points 10, 20, and 30 years before diagnosis. The *P* values and SEM bars are derived from the logistic regression model.

### Sensitivity Analyses

Because the urinary albumin/creatinine ratio was available at a limited number of examination cycles, expanding the definition

of CKD to include an eGFR < 60 ml/min per 1.73 m<sup>2</sup> or an albumin/creatinine ratio ≥ 30 mg/g reduced the number of cases and controls to 283 and 520, respectively. The relationship between the various risk factors and incident CKD was not materially different when using this definition (Supplemental Table 1).

### Risk Factor Clustering

Figure 4 shows the effect of combining risk factors at each time point, 10, 20, and 30 years before CKD diagnosis. There was a graded increase in CKD risk with each additional risk factor in any combination, with the largest effect being seen when three or four risk factors were present.

## DISCUSSION

### Principal Findings

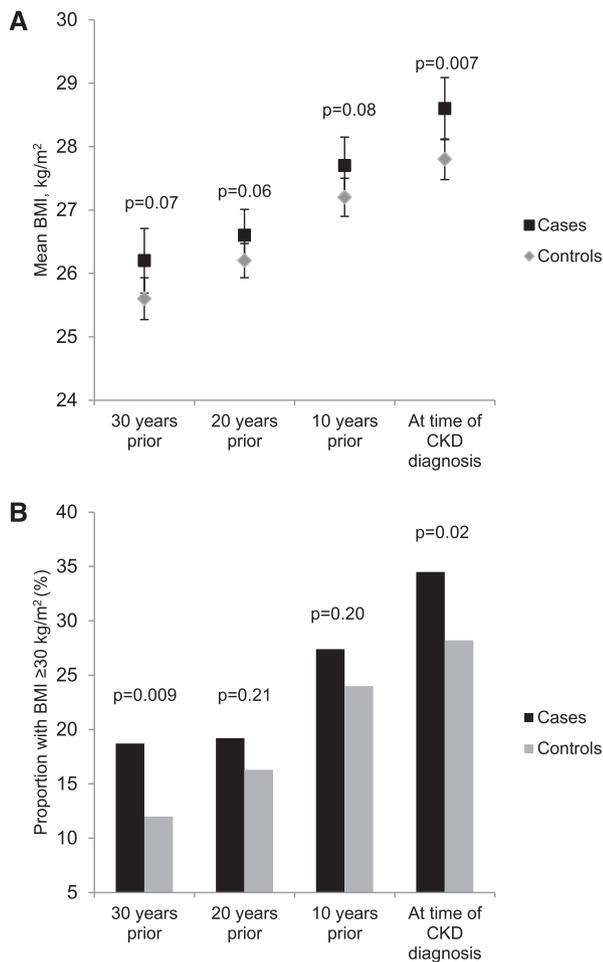
We examined known CKD risk factors in Framingham Heart Study participants who did and did not develop CKD. We found that participants who eventually developed CKD had adverse risk factor profiles up to 30 years before diagnosis compared with age- and sex-matched controls. This highlights the concept that CKD is a life course disease and that potentially modifiable risk factors for CKD are present long before clinically apparent disease has developed.

### In the Context of the Current Literature

Up to 15% of adults in the United States are estimated to have CKD, conferring an increased risk of both cardiovascular and all-cause mortality.<sup>3,4</sup> Risk factors for CKD have been well characterized,<sup>8,9</sup> but the majority of studies have evaluated risk factor profiles at or near the time of CKD diagnosis. Patients are often unaware that they have CKD,<sup>5</sup> because it is generally asymptomatic until later stages when strategies to prevent progression may be less effective.<sup>10</sup>

The importance of the presence of risk factors in early adulthood has been demonstrated previously in studies of patients with cardiovascular disease. Higher serum cholesterol in the third decade of life was associated with an increased risk of cardiovascular disease up to 30 years later.<sup>11</sup> Similarly, young adults with adverse risk factor profiles were found to have higher coronary artery calcification scores in middle age, a surrogate marker for cardiovascular disease.<sup>12</sup> A recent study found that the lifetime risk of cardiovascular disease was higher in individuals with at least one major risk factor at age 45 years. Importantly, after long-term follow-up, the maintenance of risk factor-free status was associated with a significantly decreased risk of cardiovascular morbidity.<sup>13</sup>

Our study similarly demonstrated that adverse risk factor profiles are present throughout adulthood in participants who go on to develop CKD. Those who were later diagnosed with CKD were more likely to be obese and to have hypertension and hypertriglyceridemia up to 30 years before diagnosis. Diabetes was also associated with future CKD and was present in a higher



**Figure 3.** Measures of body mass and obesity in cases and controls up to 30 years prior to CKD diagnosis. Comparison of the mean BMI (A) and the proportion of participants with obesity (B) in cases and controls at the time of CKD diagnosis and at time points 10, 20, and 30 years before diagnosis. The *P* values and SEM bars are derived from the logistic regression model.

proportion of cases from 20 years before diagnosis. Thus, in common with cardiovascular disease, our data demonstrate that CKD is a life course disease with elevation of risk factors many years before the appearance of clinically apparent disease.

### Potential Mechanisms

Individuals who later developed CKD had a higher prevalence of potentially modifiable risk factors in early adulthood. Obesity has been associated with both incident CKD and a higher rate of GFR decline in patients with established CKD.<sup>14</sup> Obesity-related glomerulopathy is characterized by the presence of glomerulomegaly or secondary FSGS on renal biopsy.<sup>15</sup> The prevalence has been increasing with growing rates of obesity in the general population.<sup>15</sup> Histopathologic changes of obesity-related glomerulopathy were noted in obese patients with no evidence of renal disease.<sup>16</sup> Successful weight loss in patients with obesity-related kidney disease was associated with a reduction in glomerular hyperfiltration and albuminuria.<sup>17,18</sup> In our study, obesity was a predictor of future CKD up to 30 years before diagnosis. However, this effect was attenuated at time points closer to CKD diagnosis. This supports recent data suggesting that obesity in early adulthood was more strongly associated with CKD in later life than obesity that developed later.<sup>19</sup> It is possible that the duration of exposure to this risk factor could play an important role in determining the magnitude of the association with CKD.

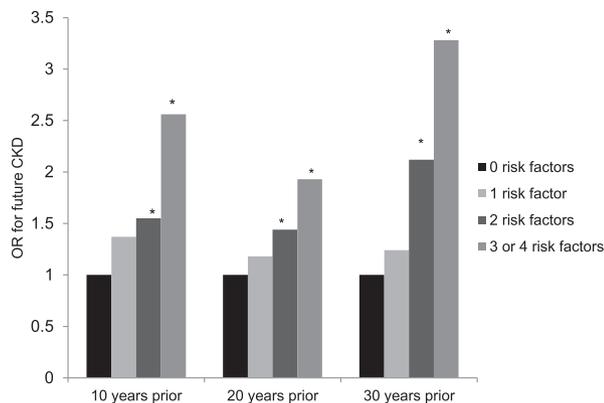
Hypertension is an established risk factor for CKD and, in common with other studies, participants who later developed CKD were more likely to be hypertensive early in life.<sup>20,21</sup> Hypertension treatment was also associated with an increased risk of future CKD. Although it might be expected that treatment of hypertension would reduce the risk of CKD, this is generally not the case in observational studies in which treatment is generally associated with increased risk as a result of indication bias. The low proportion of individuals who achieve BP targets may also contribute to this finding.<sup>22,23</sup>

**Table 2.** ORs of CKD by risk factors in the Framingham Heart Study

Risk Factor	Timing of Risk Factor Measurement					
	10 yr before CKD Diagnosis		20 yr before CKD Diagnosis		30 yr before CKD Diagnosis	
	OR (95% CI)	<i>P</i> Value	OR (95% CI)	<i>P</i> Value	OR (95% CI)	<i>P</i> Value
Systolic BP, per 10 mmHg	1.12 (1.05 to 1.20)	<0.001	1.09 (1.01 to 1.17)	0.03	1.22 (1.10 to 1.35)	<0.001
Diastolic BP, per 5 mmHg	1.05 (0.99 to 1.12)	0.10	1.07 (1.00 to 1.13)	0.04	1.18 (1.09 to 1.28)	<0.001
Hypertension	1.64 (1.29 to 2.08)	<0.001	1.38 (1.07 to 1.79)	0.01	1.76 (1.23 to 2.51)	0.002
Hypertension treatment	1.74 (1.35 to 2.24)	<0.001	1.65 (1.14 to 2.40)	0.01	1.85 (0.90 to 3.79)	0.09
LDL, per 10 mg/dl	1.00 (0.97 to 1.04)	0.97	1.00 (0.96 to 1.03)	0.86	1.02 (0.97 to 1.07)	0.43
HDL, per 10 mg/dl	0.90 (0.82 to 0.98)	0.01	0.89 (0.81 to 0.97)	0.01	0.95 (0.85 to 1.07)	0.39
Log triglycerides, mg/dl	1.26 (1.03 to 1.55)	0.03	1.35 (1.11 to 1.64)	0.003	1.43 (1.12 to 1.83)	0.01
Diabetes	1.66 (1.16 to 2.38)	0.01	2.90 (1.59 to 5.29)	<0.001	1.63 (0.43 to 6.15)	0.48
Proteinuria	1.20 (0.88 to 1.64)	0.24	1.48 (0.81 to 2.69)	0.20	<sup>a</sup>	<sup>a</sup>
Smoking	1.06 (0.78 to 1.43)	0.72	1.05 (0.81 to 1.36)	0.71	1.20 (0.88 to 1.64)	0.24
BMI, per 5 kg/m <sup>2</sup>	1.12 (0.99 to 1.27)	0.08	1.15 (0.99 to 1.32)	0.06	1.21 (0.99 to 1.47)	0.06
BMI ≥30 kg/m <sup>2</sup> (versus <30 kg/m <sup>2</sup> )	1.19 (0.91 to 1.54)	0.20	1.22 (0.90 to 1.64)	0.21	1.71 (1.14 to 2.59)	0.01

ORs are adjusted for age, sex, and calendar year of CKD diagnosis.

<sup>a</sup>Measurement not available.



**Figure 4.** OR of CKD by number of risk factors at time points 10, 20, and 30 years before CKD diagnosis. Risk factors include diabetes, hypertension, smoking, and obesity and the analysis is adjusted for age, sex, and calendar year of CKD diagnosis. \* $P < 0.05$  (significant difference from referent values; 0 risk factors).

Thus, hypertension treatment is a proxy for hypertension and as such is included in the Framingham cardiovascular disease risk score.<sup>24</sup>

Participants in this study who developed CKD were more likely to have dyslipidemia earlier in life. Dyslipidemia has been associated with an increased risk of incident CKD.<sup>25</sup> Reduced activity of lipoprotein lipase in CKD is an important mechanism for the increase in triglycerides that is commonly seen in these patients.<sup>26</sup> The accumulation of both triglycerides and the breakdown products of lipid metabolism in the blood of patients with CKD also has potent atherogenic and proinflammatory effects on the vasculature in the kidney and beyond the renal parenchyma.<sup>27</sup>

The presence of elevated CKD risk factors in mid-adulthood illustrates the importance of time in the assessment of risk factor exposure. Both the duration of exposure and the particular time of life at which one is exposed to a particular risk factor may play a role in future CKD. The importance of long-term exposure to risk factors was demonstrated in patients with cardiovascular disease.<sup>28,29</sup> The finding that clustering risk factors lead to a graded increase in the risk of future CKD suggests that the accumulation of risk factors over time, which may or may not be independent, may also play a role.<sup>30</sup> It is also possible that there are critical periods during life in which exposure to a specific risk factor may have more relevance than during other periods.<sup>30</sup>

### Implications

After the diagnosis of CKD, aggressive management of risk factors is recommended both to retard CKD progression and to reduce the risk of cardiovascular disease.<sup>31</sup> Despite this, the intensive management of risk factors, including hypertension,<sup>32,33</sup> diabetes,<sup>34,35</sup> and hyperlipidemia,<sup>36</sup> have not been consistently shown to delay the progression of disease in clinical trials.

It is possible that earlier identification and management of risk factors could be more successful at preventing the onset and progression of CKD. We have shown that these risk factors are present decades before the diagnosis of CKD. Thus, risk factor modification near the time of CKD diagnosis takes place in the setting of potential prior long-term exposure to these risk factors when aggressive management may be too late to prevent disease progression. The concept of a life course approach to the management of chronic diseases such as diabetes and cardiovascular disease is well established.<sup>37,39</sup> Elevated risk factors in early adulthood and middle age have been shown to predict future cardiovascular events.<sup>39,40</sup> Conversely, individuals who maintain an optimal risk factor profile at an early age have a low lifetime risk of cardiovascular disease.<sup>13</sup>

Our results suggest that CKD should also be considered a life course disease. Identifying individuals at increased risk of CKD early in life may allow interventions that reduce the risk of CKD. In particular, individuals with multiple risk factors could be targeted for more aggressive risk factor management. The effectiveness of such strategies is currently unknown and future studies could focus on whether early risk factor modification will decrease the incidence of CKD.

### Strengths and Limitations

The extensive phenotyping and long follow-up of the Framingham Heart Study Offspring cohort is a key strength of this study. The participants were relatively young at the time of entry into the study and were followed for up to 30 years, which allows us to generalize our results across a wide age range. However, there are some limitations that warrant mention. The sample was entirely of European ancestry, which may limit the generalizability of the results to other ethnic or racial groups. The observational nature of the data means that we cannot infer causality. Information on other potential risk factors for CKD, including physical activity, dietary factors, and socioeconomic status, were available at only one time point and therefore longitudinal comparisons were not possible. CKD was defined based on a single creatinine measurement at one time point and the majority of participants did not have creatinine measurements at the earliest examination visits. This could potentially lead to misclassification. The long duration of follow-up introduces the potential for survivorship bias. However, this would tend to bias the results toward the null.

Up to 30 years before diagnosis, risk factors for CKD are present in participants who ultimately developed CKD. The presence of adverse risk factor profiles, including potentially modifiable risk factors such as obesity, hypertension, and dyslipidemia, is notable throughout life in participants who later develop CKD. CKD is a lifetime disease and these findings emphasize the importance of the early identification of risk factors.

### CONCISE METHODS

#### Study Sample

The participants were drawn from the Framingham Study Offspring cohort. The offspring cohort began enrolling in 1971 and included the

children and spouses of the original cohort.<sup>41</sup> Participants were assessed in 4- to 8-year cycles and the assessment included a physician interview, a physical examination, and an assessment of cardiovascular disease risk factors.

For this analysis, we designed a prospective, nested, case-control study using offspring examination 5 (1991–1995) as the baseline. A case-control design was selected so that we could match for age and sex. Participants were eligible for inclusion into the study sample if they were free of CKD at baseline. Cases were defined as any new diagnosis of CKD at examinations 6, 7, or 8 (1995–2008). CKD was defined using the Chronic Kidney Disease Epidemiology Collaboration equation<sup>42</sup> as an eGFR of  $<60$  ml/min per  $1.73$  m<sup>2</sup>. Each CKD case was matched to two controls by sex and age (within 2 years) at the examination cycle of the CKD diagnosis. Risk set sampling was used to select the controls. All participants who did not have CKD at the time of diagnosis were eligible to act as controls, meaning that participants who were controls at earlier periods could be cases at a later time point.<sup>43</sup> The final sample size was 441 cases and 882 controls. From this total, 441 cases and 880 controls had risk factor measurements 10 years before CKD diagnosis, 433 cases and 866 controls had measurements at 20 years before CKD diagnosis, and 232 cases and 519 controls had measurements 30 years before CKD diagnosis. A sensitivity analysis was performed that defined CKD as an eGFR  $<60$  ml/min per  $1.73$  m<sup>2</sup> or defined albuminuria as a urinary albumin/creatinine ratio  $\geq 30$  mg/g. This study was approved by the Institutional Review Board at Boston University and all participants provided written informed consent.

### Renal Indices Assessment

Serum creatinine was measured at each cycle using the modified Jaffé method. Because variations can occur in creatinine measurements in different laboratories, this measurement was calibrated using a two-step process. First, serum creatinine values from the Third National Health and Nutritional Examination Survey (NHANES III) were calibrated to the Cleveland Clinic standard using a correction factor of 0.23 mg/dl.<sup>44</sup> Second, the serum creatinine values from our study were calibrated by alignment with age- and sex-specific means from NHANES III. The presence of proteinuria was assessed using urine dipstick tests (Labstix; Ames, Elkhart, IN) on spot urine samples collected during each visit. Proteinuria was defined as the presence of trace or more protein on dipstick testing. The urine albumin/creatinine ratio was measured on spot morning urine samples. Urinary albumin was measured using turbidimetry (Tina Quant albumin assay; Roche Diagnostics) and urinary creatinine was measured using the modified Jaffé method. Microalbuminuria was defined as an albumin/creatinine ratio of  $\geq 30$  mg/g.

### CKD Risk Factor Measurement

CKD risk factors, including systolic BP, diastolic BP, HDL<sub>c</sub>, LDL, triglycerides, dipstick urinary protein, fasting blood sugar, creatinine, and BMI (calculated by dividing weight in kilograms by height in meters squared), were measured at each examination cycle. Systolic BP and diastolic BP were recorded as the average of two measurements performed by a physician. Hypertension was defined as a systolic BP of  $\geq 140$  mmHg, a diastolic BP of  $\geq 90$  mmHg, or treatment

with antihypertensive medications. Diabetes was defined as a fasting blood glucose of  $\geq 126$  mg/dl or diabetes treatment. Current smokers were defined as those who smoked  $\geq 1$  cigarette daily over the past year. Obesity was defined as a BMI of  $\geq 30$  kg/m<sup>2</sup>.

### Statistical Analyses

For the purpose of this analysis, each risk factor was assessed at time points 30, 20, and 10 years before CKD diagnosis. At each time point, the risk factor measurement closest to this time was selected where available. CKD risk factors in the cases and their matched controls were compared using standard descriptive statistics; continuous variables were expressed as means (SDs) or medians (IQRs) where appropriate, whereas categorical variables were expressed as  $n$  (%).

To test the association between these risk factors and the future diagnosis of CKD, logistic regression models, adjusted for the matching factors (age and sex), were constructed to calculate ORs and 95% CIs for the association between each risk factor and future CKD at each time point between cases and controls. The logistic regression models were adjusted for the matching factors only (age and sex) because the risk factors we investigated are known to be independently associated with CKD. The  $P$  values in the figures were derived from the logistic regression models.

Finally, we tested whether clustering risk factors at each time point was associated with an increased risk of future CKD. To do this, we constructed logistic regression models adjusted for age and sex to calculate the OR for the association between any combination of risk factors (diabetes, hypertension, smoking, and obesity) and CKD. All analyses were conducted using SAS version 9.2 (Cary, NC) and a  $P$  value of  $<0.05$  was considered significant.

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### DISCLOSURES

None.

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