ORIGINAL RESEARCH

Contributions of Increasing Obesity and Diabetes to Slowing Decline in Subclinical Coronary Artery Disease

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***Background*—**Our previous study of nonelderly adult decedents with nonnatural (accident, suicide, or homicide) cause of death (96% autopsy rate) between 1981 and 2004 revealed that the decline in subclinical coronary artery disease (CAD) ended in the mid-1990s. The present study investigated the contributions of trends in obesity and diabetes mellitus to patterns of subclinical CAD and explored whether the end of the decline in CAD persisted.

***Methods and Results*—**We reviewed provider-linked medical records for all residents of Olmsted County, Minnesota, who died from nonnatural causes within the age range of 16 to 64 years between 1981 and 2009 and who had CAD graded at autopsy. We estimated trends in CAD risk factors including age, sex, systolic blood pressure, diabetes (qualifying fasting glucose or medication), body mass index, smoking, and diagnosed hyperlipidemia. Using multiple regression, we tested for significant associations between trends in CAD risk factors and CAD grade and assessed the contribution of trends in diabetes and obesity to CAD trends. The 545 autopsied decedents with recorded CAD grade exhibited significant declines between 1981 and 2009 in systolic blood pressure and smoking and significant increases in blood pressure medication, diabetes, and body mass index $\geq$30 kg/m^2. An overall decline in CAD grade between 1981 and 2009 was nonlinear and ended in 1994. Trends in obesity and diabetes contributed to the end of CAD decline.

***Conclusions*—**Despite continued reductions in smoking and blood pressure values, the previously observed end to the decline in subclinical CAD among nonelderly adult decedents was apparent through 2009, corresponding with increasing obesity and diabetes in that population. **(*J Am Heart Assoc*. 2015;4:e001524 doi: 10.1161/JAHA.114.001524)**

Key Words: atherosclerosis • coronary artery disease • diabetes mellitus • obesity • subclinical atherosclerosis risk factor

The marked decline in coronary artery disease (CAD) mortality in the United States since the mid-1960s has been heralded as one of the greatest public health achievements of the past 50 years. Decreases in mortality in the United States and other developed countries have been accompanied by declining hospitalizations for myocardial infarction.[1,2] These reductions in heart disease morbidity and mortality are attributed both to improved treatment among persons with advanced disease and to reductions in CAD risk factors within the population in general.[3–5]

Encouraging decreases in smoking, hypertension, and hypercholesterolemia have been accompanied more recently by the twin epidemics of obesity and diabetes mellitus,[6] raising concerns that the 5 decades of declining heart disease morbidity and mortality may soon end.[7–12] Reductions in heart disease deaths and hospitalizations, however, have continued generally unabated,[3,13–15] reinforcing the suggestion that the epidemic of obesity and associated increases in diabetes have had little impact on CAD prevalence.[16–19]

This optimism may be premature.[8] Although marked decreases in heart disease mortality over the past several decades are undisputed, a few investigations reveal a slowing of decline in recent years for certain age groups in some populations.[7,11,20] Caution against complacency is heightened because, although the vast majority of CAD deaths and

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An accompanying Appendix S1 is available at http://jaha.ahajournals.org/content/4/4/e001524/suppl/DC1

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hospitalizations occur among elderly individuals, the greatest percentage increases in obesity and diabetes have been within younger age groups.[9,21,22] In addition, because the contributions of obesity and diabetes to heart disease risk increase with duration, the adverse consequences are magnified with younger age at onset.[23–25] Consequently, the effects of obesity and diabetes on clinical outcomes of death and hospitalizations may not yet be apparent because heart disease among younger persons is typically subclinical.

These observations highlight the need to assess temporal trends in subclinical disease and the impact of temporal changes in CAD risk factors on subclinical CAD trends. Although noninvasive measures of subclinical CAD (eg, computed tomography coronary angiography and coronary artery calcium) are increasingly available,[14] to our knowledge, no temporal trend data on younger individuals have been published. Although autopsy studies may provide some information on long-term trends in grade of atherosclerosis,[26,27] autopsy rates are typically very low and have declined in recent years; therefore, most studies are subject to serious selection bias.[28] The result is that opportunities to reliably estimate long-term population-based trends in subclinical heart disease are extremely limited.

We previously took advantage of unique Rochester Epidemiology Project (REP) resources to identify a population-based sample of all nonelderly residents of Olmsted County, Minnesota, who died from nonnatural causes (accident, homicide, suicide) between January 1, 1981, and December 31, 2004. The autopsy rate for this group was extremely high (>95%) and stable over time. Review of grade of atherosclerosis at autopsy revealed a significant decline in grade over the full time period; however, for each main coronary artery, there was significant evidence ($P \leq 0.1$) that the decline ended in the mid-1990s and some suggestion ($P=0.06$) in at least 1 main coronary artery that grade of atherosclerosis was increasing after 2000.[29] The present study updated and expanded our previous findings in nonelderly adult decedents who died from nonnatural causes to estimate the extent to which trends in obesity and diabetes among these individuals contributed to the slowing of declines in atherosclerosis from 1981 through 2009.

Methods

Design, Setting, and Resources

This population-based historical cohort study of long-term trends in the prevalence of CAD and CAD risk factors was conducted in Olmsted County, Minnesota. The capability for such studies results from a unique set of circumstances. Rochester, the county seat (2010 census 144 248 residents), is ≈80 miles from the nearest major metropolitan area and is home to Mayo Clinic, one of the world's largest medical centers. Mayo Clinic, together with Olmsted Medical Center (OMC), a second group practice, and their affiliated hospitals, provide essentially all medical care received by local residents.

Since 1907, every Mayo Clinic patient has been assigned a unique identifier. Detailed information from every contact (office, nursing home, emergency department, hospital inpatient and outpatient) is contained within a unit record for each patient. Information includes general histories; physical examinations; specialty visits; laboratory, pathology, radiology, and autopsy reports; and copies of death certificates. Diagnoses assigned at each visit are coded and entered into continuously updated files. Under the auspices of the REP, the unique identifiers, diagnostic indexes, and record linkage were expanded to include OMC and the few private practitioners in the area.[30] Recent enhancements essentially afforded enumeration of all Olmsted County residents on any given date from 1966 forward.[31]

All autopsies performed on Olmsted County residents who died in Olmsted County were conducted in Mayo Clinic's Department of Laboratory Medicine and Pathology using a uniform and comprehensive system of autopsy techniques.[26] Death certificates for almost all county residents cared for by Mayo Clinic physicians were completed by the medical examiner or a Mayo Clinic autopsy pathologist. Infrequently, death certificates were completed by oncologists for hospice patients and internists for nursing home patients. Death certificates for patients cared for by physicians affiliated with other institutions (eg, OMC) were completed by their physicians. The entire medical record was reviewed; autopsy findings took precedence over clinical information.

Subjects

The present investigation was approved by Mayo Clinic and OMC institutional review boards. We used REP resources, including Minnesota state electronic death certificates and death tapes, to identify all Olmsted County residents within the age range of ≥16 to <65 years who died in the county from January 1, 1981, through December 31, 2009. Deaths were categorized as natural or nonnatural using the check box on all county death certificates that queries whether manner of death was accident, homicide, suicide, or could not be determined. When blank (ie, natural), manner of death was verified by reviewing all causes of death, as recorded on the death certificate. Another variable on all county death certificates (autopsy, yes or no) was used to identify those nonnatural deaths that were autopsied. Medical records (including autopsy reports) were reviewed to confirm that the heart was evaluated at autopsy. The present study was limited to the subset of all nonelderly adult decedents with nonnatural manner of death who had not refused authorization for

use of medical records in research[32] and for whom information on grade of coronary atherosclerosis was recorded at autopsy.

Data Collection

CAD risk factors

REP provider-linked medical records of each person were reviewed to confirm date of birth, sex, race, Hispanic origin, Olmsted County location of death, and residency at time of death and to determine the date the person was last seen by a REP provider. Manual record review was conducted by an experienced registered nurse abstractor (J.A.E.) trained in the use of medical records data for research and under the supervision of an experienced cardiovascular specialist (V.L.R.). Records were reviewed for outpatient systolic and diastolic blood pressure values and laboratory glucose and cholesterol and triglyceride values. Measures closest to death were recorded, together with whether the patient was on medication for the treatment of hypertension, diabetes, or hyperlipidemia at time of measurement. Information closest to death was also recorded on height, weight, smoking status, and alcohol use. Cardiac procedures (angiography, percutaneous transluminal coronary angioplasty with or without a stent, or coronary artery bypass grafting) and date of the most recent procedure before death were obtained electronically or with record review. All clinical diagnoses of diabetes and hyperlipidemia were also obtained, and the closest diagnosis date on or before death was recorded. For this study, diabetes was defined as fasting glucose $\geq$7.0 mmol/L or any evidence of antidiabetic medication use (oral or insulin). Body mass index was calculated as weight in kilograms divided by height in square meters. Obesity was defined as body mass index $\geq$30 kg/m^2. Lipid values were not consistently available for this age range (16 to 64 years) in this time frame (1981–2009). Only half of study subjects had total cholesterol (54%) or triglyceride (52%) measurements available. The proportions with values available dropped even further for HDL (33%) and LDL (26%). Consequently, the definition of hyperlipidemia was limited to a clinical diagnosis of hyperlipidemia within the medical record or any evidence of antihyperlipidemia medication use (statin or nonstatin). Categorizations of CAD risk factors used in analyses are provided in Tables 1 and 2.

Determination of CAD

One of the authors (P.N.N.) reviewed all autopsy records of nonnatural deaths, including the complete pathology reports, and recorded the grade assigned to each major epicardial coronary artery: left anterior descending, left circumflex, right coronary artery, and left main artery. Grades ranged from 0 (no reduction in cross-sectional luminal area) to 4, with 1, 2, 3, and 4 defined as >0% to 25%, 26% to 50%, 51% to 75%, and 76% to 100%, respectively.

Analysis

Temporal trends in CAD grade

As part of the present study, we updated our previous study of autopsied decedents from January 1, 1981, through December 31, 2004,[29] by extending the period under study through December 31, 2009. We investigated whether our previous finding of a slowing decline in CAD grade was still apparent by initially considering linear regression models for each calendar year. We then used 2-segment linear regression models with a change point (fit using nonlinear least squares regression) to explore whether CAD grade trends may have changed significantly over time. We limited the change point to calendar years 1984 through 2006 to avoid an increase in type I error due to the change point falling in the tails of the data. An F test on 2 numerator degrees of freedom was used to compare the linear regression and 2-segment linear regression models to determine whether the 2-segment model significantly improved over the linear model. Using the categorization of grades 0 to 4 described above, analyses considered the mean CAD grade across all 4 arteries combined for each decedent. Age and sex were included as adjusting variables in both linear and nonlinear models.

The estimated changes in CAD over all calendar years 1981 through 2009 were calculated by multiplying the length of the study period (29 years) by the regression estimates of temporal change from the linear regression model and the regression estimate prior to the change point (eg, 1981–1994) from the 2-segment linear regression model. The corresponding confidence intervals were similarly calculated.

CAD risk factors

Subject characteristics were summarized using descriptive statistics. Temporal trends were estimated using linear regression models with each risk factor as a dependent variable. We also investigated nonlinear temporal trends using the 2-segment linear regression model and change points described above. The models for age and sex were unadjusted. Age and sex were included as adjusting variables in both linear and nonlinear models for all other risk factors.

Associations of CAD risk factors with CAD grade

We used univariable and multivariable linear regression to estimate the joint relationship of selected risk factors with mean CAD grade over all calendar years 1981–2009 combined. Nonlinear effects of continuous terms (eg, age, blood pressure) were considered using 2-segment linear

Table 1. Characteristics of All Members of the NonElderly Adult Population of Olmsted County, Minnesota, Who Died From NonNatural Causes, 1981–2009, and Had CAD Graded at Autopsy

CAD Risk Factor	Total (n=545)
Age at death, mean (SD)	37.0 (14.0)
Sex, male, n (%)	411 (75.4)
Race, nonwhite, n (%)	49 (9.0)
Days from last visit to death, mean (SD)	258.7 (639.3)
Closest blood pressure, mm Hg, n	496
Systolic, mean (SD)	123.9 (17.1)
Diastolic, mean (SD)	76.2 (11.9)
Blood pressure medication use, n (%)	
Unknown	51 (9.4)
No	423 (77.6)
Yes	71 (13.0)
Diabetes, n (%)*	
Unknown	167 (30.6)
No	347 (63.7)
Yes	31 (5.7)
BMI, kg/m^2, n (%)	
Unknown	52 (9.5)
Underweight (<18.5)	25 (4.6)
Normal (18.5 to 24.9)	198 (36.3)
Overweight (25.0 to 29.9)	168 (30.8)
Obese (≥30.0)	102 (18.7)
Smoking status, n (%)	
Not mentioned	68 (12.5)
Never	151 (27.7)
Former	96 (17.6)
Current	230 (42.2)
Alcohol use, n (%)	
Not mentioned	65 (11.9)
Never	63 (11.6)
Former	106 (19.4)
Current	311 (57.1)
Hyperlipidemia, n (%)†	65 (11.9)
Manner of death, n (%)	
Could not be determined	19 (3.5)
Homicide	28 (5.1)
Suicide	200 (36.7)
Accident	298 (54.7)

Continued

Table 1. Continued

CAD Risk Factor	Total (n=545)
CAD grade, mean (SD)	
Overall (n=545)‡	1.1 (0.9)
LMCA (n=539)	0.9 (0.7)
LAD (n=545)	1.4 (1.1)
LCx (n=543)	1.1 (0.9)
RCA (n=540)	1.2 (1.0)

BMI indicates body mass index; CAD, coronary artery disease; LAD, left anterior descending artery; LCx, left circumflex artery; LMCA, left main coronary artery; RCA, right coronary artery.
*Fasting glucose ≥7.0 mmol/L or any evidence of antidiabetic medication use (oral or insulin).
†Clinical diagnosis of hyperlipidemia or any evidence of antihyperlipidemia medication use (statin or nonstatin).
‡Calculated for each person as the mean grade of CAD across all 4 major epicardial coronary arteries.

regression, as described above. For the multivariable models, all 2-way interactions were tested.

Estimating contributions of obesity and diabetes to temporal trends in CAD

To estimate these contributions, we considered (1) the way in which the proportion with each condition changed linearly over the full time period (1981–2009) and (2) the linear association of each condition with CAD grade. To estimate the change in the proportion with each condition, we multiplied the linear regression estimates of temporal change per calendar year by 29 years, the length of the study period, for obesity and diabetes separately. We then multiplied these change estimates by the corresponding cross-sectional estimates of the linear associations of these conditions with CAD grade from the multivariable model including calendar year (presented in Table 4). The standard errors (and resulting confidence intervals) of these products were estimated using the delta method as applied to the product of 2 independent estimates (temporal trend and association with CAD grade).

Results

There were 669 Olmsted County residents aged ≥16 to <65 years who died in Olmsted County from nonnatural causes between January 1, 1981, through December 31, 2009. Of those, 30 (4.5%) were not autopsied. Of those autopsied, 75 had no CAD grade recorded (eg, chest wound, burn), 9 had no information in their medical record before death, 9 declined research authorization, and 1 was found on record review not to be a resident of Olmsted County. Thus, 124 decedents were excluded from the analysis.

Table 2. Age- and Sex-Adjusted Temporal Trends in CAD Risk Factors*

CAD Risk Factor	Temporal Trend		
	n	Year Estimate† (95% CI)	*P* Value
Age at index	545	0.061 (−0.075 to 0.197)	0.378
Male sex	545	0.002 (−0.003 to 0.006)	0.457
Nonwhite race	545	0.004 (0.002 to 0.007)	0.002
Systolic blood pressure, mm Hg	496	−0.204 (−0.365 to −0.044)	0.013
Diastolic blood pressure, mm Hg	496	−0.180 (−0.294 to −0.066)	0.002
Blood pressure medication use	494	0.002 (−0.001 to 0.006)	0.149
Diabetes‡	545	0.002 (−0.0001 to 0.004)	0.068
Obesity§	493	0.006 (0.002 to 0.010)	0.003
Smoking‖			
Current vs former	326	−0.006 (−0.011 to −0.0004)	0.035
Ever vs never	545	0.005 (0.001 to 0.010)	0.029
Alcohol use‖			
Current vs former	417	−0.009 (−0.013 to −0.004)	<0.001
Ever vs never	545	0.002 (−0.002 to 0.006)	0.275
Hyperlipidemia¶	545	0.008 (0.005 to 0.011)	<0.001

BMI indicates body mass index; CAD, coronary artery disease.
*Models for age and male sex are unadjusted. All others are adjusted for both age and sex.
†Calendar year is defined as year of death from 1 (1981) through 29 (2009).
‡Fasting glucose ≥7.0 mmol/L or any evidence of antidiabetic medication use (oral or insulin). Modeled as diabetes vs not diabetes (including no and unknown).
§Modeled as obese (BMI ≥30 kg/m^2) vs nonobese (BMI <30 kg/m^2; including underweight, normal, and overweight).
‖Modeled as current vs former, excluding those with no known history, and as ever (including current and former) vs never (including never and not mentioned).
¶Clinical diagnosis of hyperlipidemia or any evidence of antihyperlipidemia medication use (statin or nonstatin).

Subject Characteristics

Table 1 provides subject characteristics for the remaining 545 autopsied decedents. The overall CAD grade calculated for each decedent ranged from 0.0 to 4.0, with a mean grade of 1.1 (SD 0.9). In this time period (1981–2009) and for this age group (16 to 64 years), few persons were taking antihyperlipidemia medication (n=26, 4.8%), and few had any cardiac procedures (n=13, 2.4%). The median age at death was 36.0 years (25th percentile 24.0, 75th percentile 49.0). Most individuals were last seen at a REP provider within the year before death (n=451, 82.8%); the median time from date last seen was 36 days (25th percentile 1.0, 75th percentile 223.0). Appendix S1 provides subject characteristics for a population sample of Olmsted County residents of the same age range that were seen at a REP provider in the same time period.

Temporal Trends in CAD Grade

As with our previous publication for calendar years through 2004,[29] autopsied decedents exhibited a significant decline in age- and sex-adjusted CAD grade over the full updated time period 1981–2009 (slope −0.016, 95% CI −0.023 to −0.010, *P*<0.001). Again, there was evidence of a nonlinear trend. The estimated change point was 1994, such that CAD grade declined before that year (slope −0.042, 95% CI −0.069 to −0.014, *P*=0.003), and the trend in CAD was flat after 1994 (slope 0.002, 95% CI −0.014 to 0.018, *P*=0.79). The nonlinear trend (from 2-segment linear regression) showed significant improvement over the linear trend (*P*=0.01). There was no evidence that CAD grade was increasing in recent years (Figure).

To illustrate the difference in the temporal trends found from the linear model and the better fitting nonlinear model (ie, 2-segment model), we looked at the decline in CAD grade over the full time period 1981–2009. Among autopsied decedents, the age- and sex-adjusted linear decline in CAD grade over the full time period was 0.48 of a grade (95% CI 0.28 to 0.67). When considering the nonlinear effect of calendar year on CAD grade, it appears that all of the decline occurred before 1994. Had the rate of decline estimated in the 2-segment model between 1981 and 1994 continued through 2009, the decline in CAD grade over the full time period would have been 1.21 of a grade (95% CI 0.40 to 2.01).

Temporal Trends in CAD Risk Factors

As shown in Table 2, there was no significant change in sex or age at death over time; the proportion of nonwhite individuals

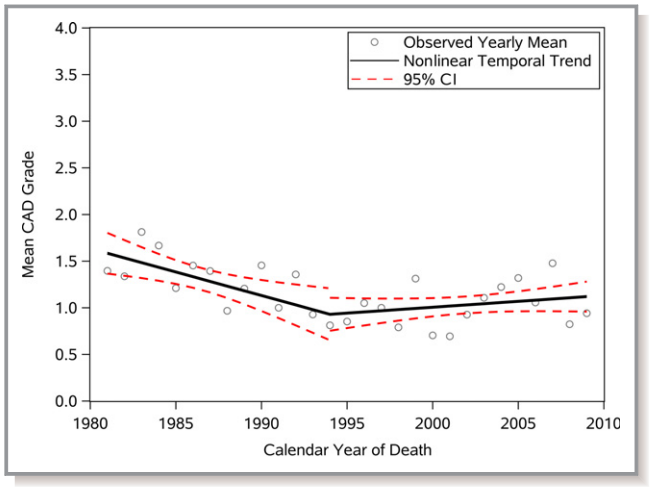

Figure. Nonlinear temporal trends in CAD grade from 1981 to 2009 for all members of the nonelderly adult population of Olmsted County, Minnesota, who died from nonnatural causes and had CAD graded at autopsy (autopsy rate 96%). CAD indicates coronary artery disease.

increased. Mean blood pressure values decreased, and antihypertension medication use increased. Among those with history of smoking or alcohol use, the proportions with current smoking and alcohol use decreased, whereas the proportion that ever smoked increased. The proportion of individuals who were obese increased, with an increase in body mass index of ≈1 unit (kg/m^2) per decade. The prevalence of diabetes approximately doubled from the first to the last decade. Significant increases were noted over time in the proportions of persons who had a clinical diagnosis of hyperlipidemia and who were on antihyperlipidemia medication (both $P<0.001$). As noted in the "Methods" section, the definition of hyperlipidemia used was limited to clinical diagnosis and medication use because the proportion of persons with lipid laboratory values was <50%. Of note, the proportions of persons with total cholesterol and triglyceride measured did not change significantly over time ($P=0.25$ and $P=0.11$, respectively), but the proportion with HDL and LDL measurements increased over the study period (both $P<0.001$) (data not shown).

There was no significant improvement in fit from linear to change point models (ie, no evidence of nonlinear temporal trends) for any CAD risk factor. Appendix S1 provides temporal trends for CAD risk factors, collected using the same protocol and definitions, for a population sample of Olmsted County residents of the same age range that were seen by a REP provider in the same time period.

Associations of CAD Risk Factors With CAD Grade

Table 3 provides results from age- and sex-adjusted univariable models of associations between CAD risk factors and CAD grade. Age at death was significantly associated with CAD grade. In this population of nonelderly adult decedents who died from nonnatural causes, sex was not significantly associated with CAD grade. Among the other CAD risk factors under consideration, ever having smoked, systolic blood pressure, diabetes, and obesity were each associated with CAD grade. These variables were included in the multivariable model, together with age and sex, and remained significant (Table 4).

We tested for nonlinear associations between each of the continuous variables (ie, age, systolic blood pressure and calendar year of death) and CAD grade. The association between systolic blood pressure and CAD grade was nonlinear, with no association below 118 mm Hg and a linear increase at or above that value. Because systolic blood pressure values <118 mm Hg were not significantly associated with CAD grade, a single variable was used to represent the nonlinear association between systolic blood pressure and CAD grade in cases in which values <118 mm Hg were set to 118. Tests for interactions between each pair of the variables and their association with CAD grade revealed 2 significant interactions. The first was between sex and diabetes such that the association between diabetes and CAD grade was greater for women ($P=0.036$). The second was between age and smoking such that, not unexpectedly, the association between smoking and CAD grade was greater at older ages of death ($P=0.039$).

Table 3. Age- and Sex-adjusted Univariable Associations Between CAD Risk Factors and CAD Grade*

CAD Risk Factor	N	Estimate (95% CI)	*P* Value
Age, y	545	0.035 (0.031 to 0.039)	<0.001
Male sex	545	0.127 (−0.043 to 0.296)	0.142
Nonwhite race	545	−0.178 (−0.389 to 0.033)	0.097
Systolic blood pressure, mm Hg†	496	0.011 (0.006 to 0.016)	<0.001
Diastolic blood pressure, mm Hg	496	0.005 (−0.0002 to 0.011)	0.058
Diabetes‡	545	0.348 (0.085 to 0.610)	0.010
Obesity§	493	0.230 (0.068 to 0.392)	0.005
Smoking‖	545	0.233 (0.108 to 0.359)	<0.001
Alcohol use‖	545	0.054 (−0.094 to 0.203)	0.475

BMI indicates body mass index; CAD, coronary artery disease.
*Models for age and male sex are unadjusted. All others are adjusted for both age and sex.
†Modeled as a nonlinear factor, that is, the association for systolic blood pressure is constant for values <118 mm Hg and increasing for values ≥118 mm Hg. The estimate represents the increase for values ≥118 mm Hg.
‡Fasting glucose ≥7.0 mmol/L or any evidence of antidiabetic medication use (oral or insulin). Modeled as diabetes vs not diabetes (including no and unknown).
§Modeled as obese (BMI ≥30 kg/m^2) vs nonobese (BMI <30 kg/m^2; including underweight, normal, and overweight).
‖Modeled as ever (including current and former) vs never (including never and not mentioned).

Of note, the multivariable model from Table 4 accounted for only 38% of variability in CAD grade among decedents. On further investigation, we found a highly significant association between calendar year of death and CAD grade, even after accounting for risk factors in the multivariable model. The residual calendar year association with CAD grade was nonlinear, with a linear decrease before 1995 and no significant association between 1995 and 2009. A single variable was used to represent the nonlinear association between calendar year and CAD grade for which years of death 1996–2009 were set to 1995. When calendar year and the significant interactions were included with other risk factors (Table 4), the resulting models accounted for 42% and 43%, respectively, of the variability in CAD grade.

The Contribution of Temporal Trends in Obesity and Diabetes to Temporal Trends in CAD Grade

We investigated whether the slowing of decline in CAD grade could be explained in part by temporal increases in diabetes

Table 4. Multivariable Associations Between CAD Risk Factors and CAD Grade

CAD Risk Factor	Excluding Calendar Year (N=473)		Including Calendar Year (N=473)		Including Calendar Year and Interactions (N=473)	
	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value
Age, y	0.030 (0.025 to 0.035)	<0.001	0.030 (0.025 to 0.035)	<0.001	0.023 (0.016 to 0.031)	<0.001
Male sex	0.083 (−0.061 to 0.228)	0.256	0.103 (−0.037 to 0.244)	0.149	0.144 (−0.00003 to 0.287)	0.050
Systolic blood pressure, mm Hg*	0.010 (0.005 to 0.016)	<0.001	0.008 (0.003 to 0.013)	0.003	0.008 (0.003 to 0.013)	0.003
Diabetes†	0.273 (0.002 to 0.543)	0.048	0.306 (0.042 to 0.569)	0.023	0.732 (0.240 to 1.224)	0.004
Obesity‡	0.166 (0.006 to 0.325)	0.042	0.224 (0.067 to 0.380)	0.005	0.214 (0.058 to 0.369)	0.007
Smoking§	0.251 (0.115 to 0.387)	<0.001	0.282 (0.149 to 0.414)	<0.001	−0.099 (−0.474 to 0.275)	0.603
Year of death‖			−0.037 (−0.051 to −0.024)	<0.001	−0.037 (−0.050 to −0.023)	<0.001
Male sex and diabetes interaction					−0.615 (−1.191 to −0.039)	0.036
Age and smoking interaction					0.010 (0.001 to 0.020)	0.039

BMI indicates body mass index; CAD, coronary artery disease.

*Modeled as a nonlinear factor, ie, the association for systolic blood pressure is constant for values <118 mm Hg and increasing for values ≥118 mm Hg. The estimate represents the increase for values ≥118 mm Hg.

†Fasting glucose ≥7.0 mmol/L or any evidence of antidiabetic medication use (oral or insulin). Modeled as diabetes vs not diabetes (including no and unknown).

‡Modeled as obese (BMI ≥30 kg/m^2) vs nonobese (BMI <30 kg/m^2; including underweight, normal, and overweight).

§Modeled as ever (including current and former) vs never (including never and not mentioned).

‖Calendar year of death from 1 (1981) through 29 (2009). Modeled as a nonlinear factor, that is, the association for year of death is decreasing for 1981–1994 and is constant for 1995–2009. The estimate represents the decrease for years 1981–1994.

and obesity, using the corresponding temporal trend estimates and the estimated associations with CAD grade.

Over the full time period (1981–2009), estimated increases in diabetes contributed an increase in CAD of 0.018 of a grade (95% CI −0.007 to 0.044). This contribution was calculated as the temporal trend estimate for diabetes (0.002) multiplied by the length of the full time period (29 years) and multiplied by the estimated association between CAD grade and diabetes (0.306). The estimated increases in obesity (1981–2009) contributed an increase in CAD of 0.040 of a grade (95% CI 0.002 to 0.078), calculated as the temporal trend estimate for obesity (0.006) multiplied by the length of the full time period (29 years) and multiplied by the estimated association between CAD grade and obesity (0.224).

Discussion

The overall decline in subclinical CAD between 1981 and 2009 revealed a nonlinear trend, with the decline limited to the first half of the 29-year period, after which the trend was flat. Findings are consistent with those from our previous study of trends for the period 1981–2004.[29] The present study examined the role of CAD risk factors in CAD grade. Importantly, examination of the contributions of temporal trends in CAD risk factors among autopsied decedents revealed that encouraging decreases in blood pressure and current smoking were countered by disconcerting increases in obesity and diabetes, contributing to an end to the decline in CAD in the mid-1990s.

Comparison With Other Studies for Temporal Trends in CAD Risk Factors and Associations With CAD

The temporal decreases in blood pressure and smoking and increases in obesity and diabetes observed in our study are consistent with trends over similar time periods reported by others.[14,33] With respect to associations between CAD risk factors and subclinical atherosclerosis among nonelderly individuals, relevant comparisons include the Bogalusa Heart studies, Pathobiological Determinants of Atherosclerosis in Youth studies, Cardiovascular Risk in Young Finns studies, Minneapolis Childhood Cohort studies, and Childhood Determinants of Adult Health studies. These studies investigated associations between CAD risk factors and atherosclerotic lesions among young adults assessed at autopsy and/or noninvasively.[34–36] Consistent with our findings, these studies found significant associations between atherosclerosis and age, smoking, blood pressure, body mass index, and hyperglycemia. To our knowledge, none of these studies published trends in subclinical CAD that included calendar years after the epidemics of obesity and diabetes began, and none explored associations between trends in CAD risk factors and trends in CAD.

Webber et al[37] studied CAD and CAD risk factors among autopsied US service members (aged 18 to 59 years, 98% male) who died from casualties during recent service in the Middle East. The authors found significant associations between CAD grade and age, obesity, and hypertension. Unlike the findings

from our study, they found no associations between CAD grade and either smoking or diabetes. Webber et al identified CAD risk factors using clinical diagnosis codes (2 outpatient or 1 inpatient) assigned within 180 days of death. The limitations of such an approach, especially for identifying behavioral risk factors such as smoking, were acknowledged by the authors and noted by others.[38,39] It is also likely that the prevalence of risk factors in their study of healthy volunteer military personnel is lower than in our study of nonnatural deaths among members of the general population.

In an effort to explore temporal trends in CAD, Webber et al[37] compared autopsy results from recent military service with previously published data on service members who died in Vietnam. They cautioned that comparisons may be confounded by differences between volunteer and conscripted individuals and by methodological differences in CAD determination. Similar to our findings for decedents over the full time period 1981–2009, Webber et al found a significant decline in CAD grade between service in Vietnam and in the Middle East.[37] The authors lacked any interim data that would afford a test for nonlinear trends between the 2 time periods corresponding to calendar years under analyses in our study.

Strengths

There is a shortage of reliable estimates of long-term trends in subclinical CAD among nonelderly adults. Our study provided population-based, 29-year trends in CAD at autopsy for a group of persons for whom the autopsy rate was very high, was consistent over time, and was essentially unrelated to CAD. The data afforded minimal autopsy selection bias. Some previous studies used data obtained from sequential population-based surveys to estimate the attributable contribution of trends in various CAD risk factors to separately obtained population event rates (eg, hospitalized myocardial infarction and death).[4,40]

Regarding longitudinal data on trends in CAD risk factors, our study had an advantage over studies that relied on diagnoses obtained from self-report or claims data. Such studies are limited by temporal changes in practice guidelines, especially for diabetes and hypertension. In contrast, our study had access to information obtained from review of detailed medical records, including standardized fasting glucose and blood pressure values and medication use. Measurements of height and weight were those recorded in the medical record. Review of smoking and alcohol use did not rely on administrative diagnosis codes but rather included both clinical mention and patient-provided self-report, as contained within the medical record. Importantly, the availability of annual estimates of CAD grade and risk factors afforded a rare opportunity to investigate nonlinear temporal trends.

Limitations

Identification of diabetes was limited to persons who ever had a fasting glucose drawn at a REP provider while a local resident; however, a relatively small proportion (22%) of nonelderly adult decedents in our study had no fasting glucose values in their medical record during the time period of interest, and of those with a value, <10% qualified as having diabetes. Moreover, we investigated associations between diabetes and CAD, both including and excluding unknown diabetes in the no diabetes category; the associations were essentially identical (data not shown).

In contrast to the situation with glucose values, nearly half of these nonelderly study subjects who died between 1981 and 2009 had no lipid measures in their medical record. Consequently, the definition of hyperlipidemia was limited to persons who ever had a clinical diagnosis of hyperlipidemia within the medical record or any evidence of antihyperlipidemia medication use (statin or nonstatin). Hyperlipidemia defined in this manner was significantly associated with CAD grade after adjusting for age and sex (P=0.036) (data not shown). We chose not to include this variable in the multivariable models presented in Table 4 because, as suggested by our findings of temporal trends, the propensity for assigning a clinical diagnosis of and for treating hyperlipidemia likely changed over our study period (1981–2009), particularly after the introduction of statin medications in 1987.[41] We do not believe the observed trend in this variable accurately reflects trends in patient characteristics; however, because hyperlipidemia is a recognized risk factor for CAD, we further investigated adding this variable to our final multivariable models. When excluding calendar year, no significant association was found for hyperlipidemia (P=0.263), and the amount of CAD grade variability explained increased from 38% to 39%. After including calendar year, a significant association for hyperlipidemia was found (P=0.045), and the amount of CAD grade variability explained increased from 42% to 43% (data not shown). No additional significant interactions were detected when hyperlipidemia was included in the multivariable models.

Similarly, although the proportions of study subjects with any glucose or blood pressure measurements were much higher than that for lipid values, temporal changes in threshold guidelines for assigning a diagnosis may have influenced the frequency of measurement (or the persons targeted for such measurements). Other changes in clinical practice (eg, the manner by which blood pressure was measured) may have changed over time. The observed temporal trends in CAD risk factors may be attributed in part to these changes.

An important limitation is the assumption that associations between CAD risk factors and CAD grade observed for autopsied decedents are applicable to the general population.

There is a potential for bias because individuals with nonnatural causes of death may differ from similar members of the general population. Although our preliminary data suggest that autopsied decedents differ from nonelderly adult Olmsted County residents with respect to level of CAD risk factors, the directions and the magnitude of temporal trends in each risk factor were similar between the 2 groups (Appendix S1).

It is important to note that the final model (ie, that included calendar year and interactions) accounted for only 43% of variation in CAD grade. This indicates the possibility that unmeasured variables that were not available in this study (eg, exercise, diet, family history, socioeconomic factors) may have played roles. After age, the strongest partial association with CAD grade was for calendar year, and the other risk factors accounted for a relatively small proportion of the total variance. Because calendar year cannot be considered a CAD risk factor directly, this suggests that there were temporal changes in unmeasured CAD risk factors.

The numbers of persons with evidence of dyslipidemia, use of antihyperlidemia medication, and surgical procedures were too small in our study to afford precise estimates of associations with temporal trends in CAD grade. Furthermore, changes in smoking behavior and blood pressure treatment may be incompletely reflected in our measurements. Although the CAD risk factors obtained through retrospective medical record review were made as uniform as possible for analysis, the information was not as standardized as data collected prospectively. The study was conducted in a single geographic area; the number of nonwhite individuals was small; and although no single geographic area is representative of all others, the extent of generalizability to the total US population cannot be determined.

Conclusions

This study of subclinical heart disease and associated risk factors among nonelderly adult decedents found that a decline in CAD grade over the full time period 1981–2009 was accompanied by significant reductions in elevated blood pressure and current smoking. Importantly, the temporal decline in CAD grade was limited to the first half of the period. After 1994, the trend in CAD was flat (P=0.79). We observed significant increases in the prevalence of obesity and diabetes in this population, and these increases likely contributed to an end in any continued decline in CAD grade from the mid-1990s forward.

These findings reinforce concerns that the obesity and diabetes epidemics may adversely affect cardiovascular morbidity and mortality and total mortality in coming years. Secondary prevention (eg, pharmacologic treatment) of obesity and associated CAD risk factors (ie, hypertension, dyslipidemia, and diabetes) can assist only so far in controlling morbidity and mortality. Any beneficial effects of treatment programs may be offset by failure to address the growing numbers of persons who are obese and diabetic. The findings presented in this study caution against complacency about the future impact of obesity and diabetes (both preventable conditions) based on current trends in CAD mortality.

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Disclosures

None.

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