Prediction of First Events of Coronary Heart Disease and Stroke With Consideration of Adiposity

Peter W.F. Wilson, MD; Samuel R. Bozeman, MPH; Tanya M. Burton, PhD; David C. Hoaglin, PhD; Rami Ben-Joseph, PhD; Chris L. Pashos, PhD

Background—Prediction of coronary heart disease (CHD) and cerebrovascular disease (CeVD) can aid healthcare providers and prevention programs. Previous reports have focused on traditional cardiovascular risk factors; less information has been available on the role of overweight and obesity.

Methods and Results—Baseline data from 4780 Framingham Offspring Study adults with up to 24 years of follow-up were used to assess risk for a first CHD event (angina pectoris, myocardial infarction, or cardiac death) alone, first CeVD event (acute brain infarction, transient ischemic attack, and stroke-related death) alone, and CHD and CeVD events combined. Accelerated failure time models were developed for the time of first event to age, sex, cholesterol, high-density lipoprotein cholesterol, diabetes mellitus (DM), systolic blood pressure, smoking status, and body mass index (BMI). Likelihood-ratio tests of statistical significance were used to identify the best-fitting predictive functions. Age, sex, smoking status, systolic blood pressure, ratio of cholesterol to high-density lipoprotein cholesterol, and presence of DM were highly related \( (P<0.01 \text{ for all}) \) to the development of first CHD events, and all of the above except sex and DM were highly related to the first CeVD event. BMI also significantly predicted the occurrence of CHD \( (P=0.05) \) and CeVD \( (P=0.03) \) in multivariable models adjusting for traditional risk factors. The magnitude of the BMI effect was reduced but remained statistically significant when traditional variables were included in the prediction models.

Conclusions—Greater BMI, higher systolic blood pressure, higher ratio of cholesterol to high-density lipoprotein cholesterol, and presence of DM were all predictive of first CHD events, and all but the presence of DM were predictive of first CeVD events. These results suggest that common pathophysiological mechanisms underlie the roles of BMI, DM, and systolic blood pressure as predictors for first CHD and CeVD events. (Circulation. 2008;118:124-130.)

Key Words: coronary disease ■ epidemiology ■ obesity ■ risk factors

The prediction of coronary heart disease (CHD) and cerebrovascular disease (CeVD) has become an area of concentrated investigation. Topics of interest for prediction include the role of the individual variables, the importance of novel risk factors, and increased utility of this approach through relatively simple characterization of the variables. On the outcome side, research has focused on standardizing the definitions and understanding how results may vary according to the specific vascular event being predicted. For instance, in the prediction of CHD, it is very important to assess lipids, blood pressure, and smoking. On the other hand, lipids are important predictors of ischemic stroke but less important for hemorrhagic stroke, and blood pressure is an important determinant of both ischemic and hemorrhagic stroke outcomes.

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The role of obesity as a risk factor for cardiovascular disease (CVD) has been controversial. In most analyses that estimate CHD risk no statistically significant effect for a measure of adiposity such as body mass index (BMI) or waist girth has been reported after adjustment for traditional risk factors such as systolic blood pressure (SBP), diabetes mellitus (DM), and high-density lipoprotein cholesterol (HDL-C). Greater adiposity frequently leads to abnormalities in several of the classic risk factors, and actual risk factor levels, not the severity of underlying adiposity, have been more tightly related to adverse cardiovascular outcomes.

We have undertaken analyses to predict the development of first CHD or CeVD events and have taken into account the issues mentioned above. The experience of the Framingham Offspring Study, with >20 years of follow-up for vascular events after a baseline examination, provided data for these analyses. To develop a better sense of the role of adiposity in mediating risk for these vascular events, we performed a variety of analyses with and without the adiposity measure BMI, which was available at the baseline examination. The
results should improve our understanding of the role of adiposity and other metabolic variables in the prediction of CHD and CeVD.

Methods

The Framingham Offspring Study began in 1971 with the recruitment of 5124 men and women who were the offspring and spouses of the participants in the original Framingham Heart Study.2 Every 4 to 8 years, the participants have undergone a history and physical examination that included laboratory testing. This analysis is based on 24 years of experience, and participants have been followed up for the development of vascular disease events with adjudication by a panel of physicians on the research team. The prediction models presented here are based on data from the initial baseline examination with surveillance for CVD events through the ensuing 5 examinations with ∼24 years of follow-up.

Of the 5124 participants who attended the baseline examination, we excluded 235 because they were <18 years of age or had a history of CVD. An additional 105 participants were not included because they had a missing value for ≥1 of the predictor variables (age, gender, smoking status, SBP, ratio of total cholesterol to HDL-C, and BMI). Four participants were lost to follow-up. These exclusions yielded a total study sample for analysis of 4780 participants. Public-use data were used for the analyses, and this study was approved by the Institutional Review Board at Abt Associates.

Baseline data included information from the history and physical examination. Persons reporting smoking cigarettes regularly during the past 12 months were considered smokers. Height and weight measurements were available to calculate BMI in kilograms per meter squared. No waist measurements were made at the baseline examination. We used SBP values from the Framingham Offspring Study data set at examination 1, and hypertension treatment was not considered in the definition of SBP. Diabetes was defined in the Framingham Offspring Study data set as being positive for one of the following at examination 1: glucose of ≥126 mg/dL or participant was receiving insulin or oral hypoglycemics. Cholesterol and HDL-C were determined according to the Lipid Clinics Program protocol as previously described.8

CHD included the following types of events and diagnoses: myocardial infarction, angina pectoris, coronary insufficiency, and CHD-related death. The CHD outcome was the time to the first CHD event. CeVD included stroke (acute brain infarction), transient ischemic attack, and stroke-related death. Consistent with prior reports of differing causes of cerebral embolisms and hemorrhagic strokes, embolisms and intracerebral and subarachnoid hemorrhagic strokes (total, n = 19) were censored in these analyses and were not counted as CeVD events. The CeVD outcome was the time to the first CeVD event. CVD was a composite measure of the CHD and CeVD events listed above and included intermittent claudication and congestive heart failure. The CVD outcome was the time to the first CVD event. Specific criteria for the clinical and laboratory methods and the event adjudication have been published previously.2,5

We used an accelerated failure time (AFT) survival model to analyze the number of days from the first examination until the first CHD, CeVD, or CVD event. The time to the first cardiovascular event was compatible with a Weibull distribution, and the SAS LIFEREG procedure was used to assess the effect of 6 predictor variables known to be associated with the outcomes according to previous Framingham research.10 The variables included in the analyses were age, sex, SBP, current smoking status, diabetic status (as defined by treatment or fasting blood glucose >126 mg/dL), and lipoprotein cholesterol levels (expressed as the ratio of total cholesterol to HDL-C).5,11 The primary goal was to assess the relative contribution of BMI in the presence of core predictor variables for CHD, CeVD, and total CVD. In parallel analyses using the Cox proportional-hazards model, we found that the data met the proportional-hazards assumption and that the parameter estimates (hazard ratios [HRs]) were equivalent between the 2 methods (analyses available on request). We chose to report the results from the AFT models to be consistent with the work of Anderson et al.12

To assess the predictive impact of the variables from a single examination, we used the measurements from the first clinic visit only, and we did not take into account any change in the values of the predictor variables during the course of the study. We assessed the relative goodness of fit of the resulting models through the log-likelihood statistic and the discriminatory ability of the models through the c statistic.3,13,14 The effects of individual predictor variables are presented as HRs associated with the presence of a risk factor or with a specified difference in levels of a risk factor. These HRs were estimated from the coefficients of the predictor variables in the AFT models.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Tables 1 and 2 present selected demographic and clinical characteristics of the participants at the baseline examination stratified by adiposity (obesity is defined as BMI ≥30). The mean age of the study subjects at baseline was 37 years, and 51.6% were women. All participants were white; 65% were former or current smokers. The mean BMI was 25.4 kg/m², close to the threshold between the normal and overweight classifications of adiposity. The distribution of BMI levels over the categories <18.5, 18.5 to 24.9, 25 to 29.9, 30 to 34.9, and ≥35.0 kg/m² was 1.7%, 49.8%, 35.1%, 10.4%, and 3.0%, respectively. Overall, ∼13.3% were obese at baseline. Study participants who were obese at baseline had higher mean values for cholesterol and SBP, were more likely to be men, were more likely to have DM, and were more likely to experience one of the outcome events. The median time to an initial CHD or CeVD event over the first 6 examinations was 12.6 and 17.6 years, respectively, among those who experienced an event.

Table 3 presents the HRs for 7 models. We fitted a variety of AFT risk models for the outcome of first CHD event. All variables of interest (sex, age, smoking status, BMI, ratio of cholesterol to HDL-C, SBP, and DM) were significant predictors of a first CHD event (P≤0.05) in each model that included them. For a 1-SD difference in BMI (4.33 kg/m²) in the full multivariable analysis (model E), the HR was 1.10.

Table 1. Baseline Characteristics of Study Sample

<table>
<thead>
<tr>
<th>Factor</th>
<th>BMI &lt;30 kg/m² (n=4143; 86.7%)</th>
<th>BMI ≥30 kg/m² (n=637; 13.3%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>36.4 (9.77)</td>
<td>39.0 (9.90)</td>
<td>36.7 (9.75)</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>53.7</td>
<td>38.0</td>
<td>51.6</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>45.6</td>
<td>42.7</td>
<td>45.2</td>
</tr>
<tr>
<td>Former smoking, %</td>
<td>19.6</td>
<td>19.9</td>
<td>19.7</td>
</tr>
<tr>
<td>BMI (mean), kg/m²</td>
<td>24.2 (2.92)</td>
<td>33.4 (3.50)</td>
<td>25.4 (4.33)</td>
</tr>
<tr>
<td>SBP (mean), mm Hg</td>
<td>120.4 (15.64)</td>
<td>134.0 (18.25)</td>
<td>122.2 (16.67)</td>
</tr>
<tr>
<td>Cholesterol (mean), mg/dL</td>
<td>195.2 (30.99)</td>
<td>206.8 (38.37)</td>
<td>196.8 (39.19)</td>
</tr>
<tr>
<td>HDL-C (mean), mg/dL</td>
<td>51.7 (14.65)</td>
<td>43.9 (13.22)</td>
<td>50.7 (14.71)</td>
</tr>
<tr>
<td>Cholesterol-to-HDL-C ratio (mean)</td>
<td>4.1 (1.53)</td>
<td>5.1 (1.81)</td>
<td>4.2 (1.61)</td>
</tr>
<tr>
<td>DM, %</td>
<td>2.0</td>
<td>8.2</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Values are mean±SD when appropriate. n=4780.
suggesting a 10% greater risk of a first CHD event for a difference of 4.33 kg/m² in BMI at baseline.

Models A through D in Table 3 show the HRs for the 4 possible combinations of the predictor variables cholesterol-to–HDL-C ratio and SBP, in addition to BMI, age, sex, and cigarette smoking. The effect estimates for all variables varied little across the models. The effect estimates of the variables cholesterol-to–HDL-C, SBP, DM (data not shown), and BMI were attenuated slightly in the full model (model E). The magnitude of the log-likelihood statistic was greatest for model E, although values varied little across the models. The effect estimates of the variables cholesterol-to–HDL-C ratio and SBP, in addition to BMI, age, sex, and cigarette smoking. The effect estimates for all variables varied little among the models. The effect estimates of the variables cholesterol-to–HDL-C, SBP, DM (data not shown), and BMI were attenuated slightly in the full model (model E).

The magnitude of the log-likelihood statistic was greatest (smallest negative number) in the full multivariable analysis (model E), although the addition of variables always increased the log likelihood. Similarly, the magnitude of the c statistic was greatest for model E, although values varied little across the models. The c statistics for 2 additional models: the core model (model A) with BMI removed and the full multivariable model (model E). That effect diminished to 1.10 in the full multivariable model (model E), which included the metabolic factors SBP, cholesterol-to–HDL-C ratio, and DM. An interpretation of this difference in the HRs between models A and E is the proportion of excess risk, found by (HRU − HRa)/ (HRU − 1), where HRa is the HR for CHD conferred by a difference in 1 SD of BMI unadjusted for DM and cholesterol and SBP levels and HRU is the adjusted HR for BMI accounting for the related variables. Thus, (1.28−1.10)/ (1.28−1) or 64% of the BMI effect appears to operate through the variables cholesterol-to–HDL-C ratio, SBP, and DM, which were included in model E but not in model A. An alternative method computes the excess in the scale of the β coefficients from the AFT models according to 1− (ln HRA/ln HRa)17 and yields a similar estimate, 61%.

Table 3 presents the HRs from the AFT models for first occurrence of CeVD. Neither sex (P=0.30) nor DM (P=0.28) was a significant predictor of CeVD events at the P<0.05 level in these models, and we did not retain those variables. The size of the effect estimate for BMI in the

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Units</th>
<th>A, No BMI</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>E, No BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td></td>
<td>4.33 kg/m²</td>
<td>1.28 (1.17–1.39)</td>
<td>1.17 (1.07–1.28)</td>
<td>1.21 (1.11–1.33)</td>
<td>1.11* (1.01–1.23)</td>
<td>1.10† (1.00–1.21)</td>
<td></td>
</tr>
<tr>
<td>Cholesterol-to–HDL-C ratio</td>
<td>1.61 Unit</td>
<td>1.38 (1.30–1.47)</td>
<td>1.38 (1.30–1.46)</td>
<td>1.37 (1.29–1.46)</td>
<td>1.39 (1.31–1.47)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>16.67 mm Hg</td>
<td>1.18 (1.08–1.27)</td>
<td>1.18 (1.09–1.28)</td>
<td>1.17 (1.08–1.28)</td>
<td>1.20 (1.11–1.30)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>Yes/no</td>
<td>1.57 (1.49–1.64)</td>
<td>1.48 (1.40–1.58)</td>
<td>1.48 (1.40–1.58)</td>
<td>1.48 (1.40–1.56)</td>
<td>1.48 (1.40–1.56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>5 y</td>
<td>0.35 (0.29–0.43)</td>
<td>0.38 (0.31–0.47)</td>
<td>0.40 (0.33–0.49)</td>
<td>0.40 (0.33–0.49)</td>
<td>0.40 (0.30–0.61)</td>
<td>0.40 (0.40–0.60)</td>
<td></td>
</tr>
<tr>
<td>Current Smoker</td>
<td>Yes/no</td>
<td>2.01 (1.68–2.41)</td>
<td>2.13 (1.78–2.55)</td>
<td>1.97 (1.64–2.38)</td>
<td>1.97 (1.64–2.38)</td>
<td>1.95 (1.63–2.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log likelihood</td>
<td>−1706.46</td>
<td>−1692.8</td>
<td>−1654.2</td>
<td>−1685.7</td>
<td>−1646.9</td>
<td>−1643.2</td>
<td>−1645.1</td>
<td></td>
</tr>
</tbody>
</table>


HRs indicate effects for the number of units specified in the table. P<0.01 for all cells except *P=0.03 and †P=0.05.

Table 2. Vascular Events and Follow-Up Characteristics of Study Sample

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Frequency of First Events, n (%)</th>
<th>Median Time to First Event, y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BMI &lt;30 kg/m² (n=4143)</td>
<td>BMI ≥30 kg/m² (n=637)</td>
</tr>
<tr>
<td></td>
<td>BMI &lt;30 kg/m² (n=4143)</td>
<td>BMI ≥30 kg/m² (n=637)</td>
</tr>
<tr>
<td>CHD*</td>
<td>381 (9.2)</td>
<td>111 (17.4)</td>
</tr>
<tr>
<td>CeVD†</td>
<td>83 (2.0)</td>
<td>28 (4.4)</td>
</tr>
<tr>
<td>CVD‡</td>
<td>534 (12.9)</td>
<td>150 (23.6)</td>
</tr>
</tbody>
</table>

n=4780.

*CHD included myocardial infarction, angina pectoris, coronary insufficiency, and CHD-related death.
†CeVD included stroke (acute brain infarction but not cerebral embolisms or intracerebral and subarachnoid hemorrhagic strokes), transient ischemic attack, and stroke-related death.
‡CVD included CHD, CeVD, intermittent claudication, and congestive heart failure.
The proportional difference in the BMI HRs is (1.35 – 1.21) or 40% indicates the contribution of the additional variables to the excess risk; ie, 40% of the BMI effect appears to operate through the combination of the variables cholesterol-to–HDL-C ratio and SBP. The alternative method yields a similar estimate, 36%. The difference in the log likelihood across the models was small relative to the CHD models, ranging from 0.80 to 0.82, suggesting excellent discriminatory power of the models. As with the CHD models, the highest values for both the log likelihood and c statistic were for the full multivariable model (model D). For comparison, we include statistics for 2 additional models: the core model (model A) with BMI removed and the full multivariable model (model D) with BMI removed. The discriminatory power and fit as measured by the c statistic and log likelihood are best for model D.

Table 5 presents the HRs from the AFT models for first occurrence of total CVD. All variables of interest (sex, age, smoking status, BMI, cholesterol-to–HDL-C ratio, SBP, and DM) were significant predictors of a first CVD event at the P<0.05 level. Both CHD and CeVD events are components of the first CVD outcome, and the number of CHD events (n=492) was higher than the number of CeVD events (n=111). The HR for a 1-SD difference in BMI (4.33 kg/m²) in the full multivariable analysis (model B) was 1.09, suggesting a 9% greater risk of a first CVD event for a 1-SD increase in BMI at baseline. For the simple analysis that included only age, sex, smoking, and BMI (model A), the HR for a 1-SD difference in BMI at baseline was 1.21, indicating a 21% greater CeVD risk for a 1-SD increase in BMI at baseline.
(1.27−1) or 67%; ie, 67% of the BMI effect appears to operate through the other variables (64% using the alternative method). The c statistic value was again highest for the full model (model B, c=0.80). For comparison, we include statistics for 2 additional models: the core model (model A) with BMI removed and the full multivariable model (model B) with BMI removed. The discriminatory power and fit as measured by the c statistic and log likelihood are virtually equivalent between model B and model B with BMI removed.

To further explore the role of BMI as a cardiovascular determinant, we undertook other analyses that considered different durations of follow-up, younger versus older participants at study entry, and weight change from baseline to the second examination (results not shown). When duration of follow-up was 6 examinations (24 years of follow-up), 3 examinations (16 years of follow-up), or 2 examinations (12 years of follow-up), we found nearly the same effects for BMI on risk of CVD outcomes. The HR of ≈1.27 for BMI in model A stayed highly statistically significant with this approach, and the HR in model B, which included full multivariable adjustments, led to little change in the HR of ≈1.07 but successive lowering in the number of events and loss of statistical significance when follow-up was either 3 or 2 examinations, suggesting lack of statistical power to show an effect. In analyses that split the population at the median age of 36 years at baseline, we found that BMI was significantly associated with CVD risk in model A at younger or older ages, but the effects were not statistically significant in the full multivariable model B (HR=1.02, P=0.15) in the younger or older groups. In addition, a weight loss or weight gain of >10 pounds between baseline and the second examination 8 years later did not have a significant effect on the vascular disease outcomes.

As a validation exercise for the results discussed above, we tested the same model in the original Framingham Heart Study cohort (n=3073) using a similar follow-up period (mean follow-up, 24 years). Dissimilarities between the 2 data sets led to 2 important differences in the analyses: We could not distinguish the type of CVD event, and only total serum cholesterol, not HDL-C, was available from examination 1 in the Framingham Heart Study. Therefore, we tested the models (simple versus multivariable) for CHD (models A through E in Table 3) only and used total cholesterol (rather than the ratio of total cholesterol to HDL) to adjust for cholesterol in assessing the effect of BMI. BMI was a significant predictor of CHD events in these data (HR=1.17; 95% CI, 1.07 to 1.28) in models that included age, sex, smoking status, DM, cholesterol, and SBP. These results from the original Framingham cohort validate the findings in the Framingham Offspring Study on BMI as an independent vascular disease risk factor with long-term follow-up.

The Appendix provides the β coefficients used in Tables 3 and 4 (models E and D, respectively) so that other investigators may use this approach to estimate risk for CHD and CeVD. The methods to calculate the absolute risk of an event over a 10-year interval are provided.

Discussion

Our results show that BMI was positively related to the long-term incidence of CHD, stroke, and total CVD in the Framingham Offspring Study. The BMI effect on CHD and CeVD risk was statistically significant, and the differences in the log-likelihood statistics among the models in Table 3 for CHD and Table 4 for CeVD were modest, as would be expected in vascular disease prediction models that included age as a covariate. The effect of BMI remained significant in models adjusted for known CVD risk factors such as cholesterol-to–HDL-C ratio, DM, and SBP, which frequently cluster in high-risk individuals and are hypothesized to share causal cardiovascular pathways with obesity. The significant BMI effect in these adjusted models may result from adiposity alone or adiposity plus unmeasured variables such as physical activity, dietary intake, C-reactive protein, inflammatory factors such as adiponectin, or other adipokines.

As mentioned in the Results after the description of the findings from Table 5, we undertook focused multivariable analyses that investigated BMI as a risk factor for CVD. We found that the BMI effects were similar at younger and older ages. Varying the duration of follow-up showed that BMI was not significantly associated with CVD over shorter (only 2 or 3 examinations) follow-up, although the HR was similar across 2, 3, or 6 follow-up examinations. This result also is consistent with a recently updated Framingham CVD prediction algorithm that used 12 years of follow-up and did not include an adiposity measure as a predictive factor. These results suggested that longer follow-up was the key reason for our finding BMI to be a significant predictor of CVD in these analyses because shorter-duration investigations are generally underpowered statistically to address this question.

In all of these models, we sought to use simple prediction models to analyze risk for initial CHD and CeVD events. We considered adding 2-factor interaction terms to each model and found that only age-by-SBP and cholesterol-to–HDL-C ratio–by-BMI were significant for CHD and CVD and that only cholesterol-to–HDL-C ratio–by-BMI was significant for CeVD. However, in each model, the addition of the interaction terms produced a negligible increase in the predictive power as assessed by the c statistic.

Higher cholesterol-to–HDL-C ratio, SBP, and DM often occur concomitantly, and including these factors alone or in combinations in our analyses tended to reduce the HR for BMI in the multivariable prediction model. For the CHD outcome, the greatest diminution of the BMI HR in Table 3 was observed when the cholesterol-to–HDL-C ratio was included (model B), and a smaller effect was seen for SBP (model C). Opposite effects were observed for CeVD in Table 4 with models B and C, in which the effect was greater for SBP.

The present study reports the long-term incidence for first CHD and CeVD outcomes in a population sample with a mean age of 37 years at the outset, reflecting the experience of adults for whom elevated adiposity may have been present during young adulthood and traditional risk factor alterations are less likely to have been present for a long time. It is interesting to hypothesize that greater adiposity in younger adults may play a stronger role in the development of CHD.
and CeVD than for middle-aged and older persons. Previous research from Framingham has shown that overweight (BMI, 25 to 30 kg/m²) and definite obesity (BMI ≥ 30 kg/m²) antedated the development of abnormal risk factor levels and modest increases in risk for CVD events. This study has limitations and reports only the experience of middle-class non-Hispanic white individuals living in a suburban environment. Our study includes adults who were younger at the baseline evaluation than in many other studies; the findings emphasize risk for the development of first CHD and first CeVD events; and the follow-up for this report was largely complete by the mid 1990s. Unfortunately, waist circumference was not measured at baseline, and it was not possible to analyze whether waist circumference was associated with altered risk of CHD and CeVD. Additionally, information related to the underpinnings of excess adiposity as reported physical activity and dietary intake were not collected at the baseline examination used for this study. Generalizing these results to other geographic regions requires consideration of age, sex, and race/ethnicity of the populations, as well as calendar year of experience because risk factor management of lipids, blood pressure, and blood glucose has become more aggressive over the past decade.

Conclusions

This study has shown that greater adiposity is related to an increased risk of CHD, CeVD, and CVD. The adiposity variable BMI remained significantly related to the development of vascular disease outcomes even after adjustment for traditional cardiovascular risk factors. A major part of the effect of adiposity on vascular disease risk appears to be mediated through cholesterol-to-HDL-C ratio, SBP, and DM.

We fit the data with an AFT survival model based on a Weibull distribution. The Weibull model yields a linear function of the predictor variables \( x_1, x_2, \ldots \), and the estimated intercept \( \hat{\beta}_0 \) and coefficients \( \hat{\beta}_1, \hat{\beta}_2, \ldots \), which we denote by

\[
L(x) = \hat{\beta}_0 + \hat{\beta}_1 x_1 + \hat{\beta}_2 x_2 + \ldots + \hat{\beta}_7 x_7
\]

along with an estimate \( \hat{\sigma} \) of the Weibull shape parameter (which determines the shape of the hazard function). (The model for time to a CHD event has 7 predictor variables, and the model for time to a CeVD event uses the first 5 variables.)

For a person with a particular combination of the predictor variables \( x \), the predicted value of the Weibull survival function at time \( t \), \( S(t) \), is given by Equation 2:

\[
S(t) = \exp\left[\exp\left(-[t \exp(-L(x))]^{\frac{1}{\hat{\sigma}}}\right)\right].
\]

The risk of an event by time \( t \) is

\[
1 - S(t).
\]

For an example of predicted time to a CHD event, we evaluate the model at the values of each variable in hypothetical vector \( x \) given in Table 6 for Equation 1 as follows:

\[
L(x) = 14.9756(\text{intercept}) + (-0.0159) \times 30(\text{BMI}) + (-0.0571) \times 60(\text{age in years}) + (-0.4959) \times 0(\text{Nonsmoker}) + (-0.0070) \times 130(\text{SBP}) + (-0.1432) \times 5.5(\text{cholesterol-to-HDL-C ratio}) + (-0.3421) \times 0(\text{Nondiabetic}) + (0.5139) \times 0(\text{Male}) = 9.3693.
\]

Inserting this value for \( L(x) \) into Equation 2 and using the value of \( \hat{\sigma} \) from the table, we have:

\[
S(t) = \exp\left[-\left[3650 \text{ days}\exp\left(-9.3693\right)\right]\right]^{0.7303} = 0.8168.
\]

The probability, then, of an individual with the assigned risk profile experiencing a CHD event over 10 years is given by Equation 3:

\[
P(\text{event in 10 years}) = 1 - 0.8168 = 0.1832.
\]

**Table 6. Individual CHD and CeVD Risk Calculation for a Hypothetical Individual With a Given Risk Profile**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Personal Characteristics for Hypothetical Example</th>
<th>CHD Model Coefficients (β)</th>
<th>CeVD Model Coefficients (β)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (x₁)</td>
<td>30</td>
<td>-0.0159</td>
<td>-0.0227</td>
</tr>
<tr>
<td>Age (x₂)</td>
<td>60</td>
<td>-0.0571</td>
<td>-0.0450</td>
</tr>
<tr>
<td>Current smoker (x₃)</td>
<td>(Nonsmoker) 0</td>
<td>-0.4959</td>
<td>-0.2584</td>
</tr>
<tr>
<td>SBP (x₄)</td>
<td>130</td>
<td>-0.007044</td>
<td>-0.007879</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>220</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>HDL-C</td>
<td>40</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cholesterol-to–HDL-C ratio (x₅)</td>
<td>5.5</td>
<td>-0.1432</td>
<td>-0.0596</td>
</tr>
<tr>
<td>Diabetic (x₆)</td>
<td>(Nondiabetic) 0</td>
<td>-0.3421</td>
<td>NA</td>
</tr>
<tr>
<td>Sex (x₇)</td>
<td>(Male) 0</td>
<td>0.5139</td>
<td>NA</td>
</tr>
<tr>
<td>Intercept (β₀)</td>
<td>1</td>
<td>14.9756</td>
<td>14.6574</td>
</tr>
<tr>
<td>Weibull Shape (S)</td>
<td>NA</td>
<td>0.7303</td>
<td>0.4978</td>
</tr>
<tr>
<td>t=10 y (days)</td>
<td>3650</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>L(x)</td>
<td>9.3693</td>
<td>9.9243</td>
<td></td>
</tr>
<tr>
<td>t exp(-L(x))</td>
<td>0.3114</td>
<td>0.1787</td>
<td></td>
</tr>
<tr>
<td>1/S</td>
<td>1.3693</td>
<td>2.0088</td>
<td></td>
</tr>
<tr>
<td>(t×exp[-L(x)]1/2)</td>
<td>0.2024</td>
<td>0.0315</td>
<td></td>
</tr>
<tr>
<td>S(t) (survival function)</td>
<td>0.8168</td>
<td>0.9690</td>
<td></td>
</tr>
<tr>
<td>P(event in 1 years)</td>
<td>1−S(t)</td>
<td>0.1832</td>
<td>0.0310</td>
</tr>
</tbody>
</table>
Table 6 provides the calculations for the probability of this same hypothetical individual experiencing a CeVD event over 10 years ($P=0.0310$).

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We acknowledge the help of Steven Sirko from sanofi-aventis for research plan development and critical review of the manuscript.

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**Disclosures**

None.

**References**


**CLINICAL PERSPECTIVE**

The key determinants of cardiovascular disease (CVD) are age, sex, cholesterol, high-density lipoprotein cholesterol, systolic blood pressure level, cigarette smoking, and diabetes mellitus. Greater adiposity generally has not been associated with the development of CVD when the traditional variables mentioned above are used to predict outcome. Data from 24 years of follow-up for the Framingham Offspring Study population sample were used to estimate the effect of body mass index (BMI) on risk of CVD. In a simple prediction model of CVD that included age, sex, and smoking, a 1-SD unit (4.33 kg/m²) of BMI imparted a 28% effect on risk of initial CVD events. After full adjustment with the traditional CVD prediction factors, the effect of an SD of BMI remained statistically significant but declined to 10%. It was estimated that 67% of the BMI effects appear to operate through the ratio of cholesterol to high-density lipoprotein cholesterol, systolic blood pressure, and diabetes mellitus. These results imply that a considerable portion of the adverse effects of BMI are exerted through traditional metabolic risk factors and that long-term follow-up of middle-aged adults was required to fully identify these effects.
Prediction of First Events of Coronary Heart Disease and Stroke With Consideration of Adiposity
Peter W.F. Wilson, Samuel R. Bozeman, Tanya M. Burton, David C. Hoaglin, Rami Ben-Joseph and Chris L. Pashos

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