ORIGINAL RESEARCH

Reducing the Population Burden of Coronary Heart Disease by Modifying Adiposity: Estimates From the ARIC Study

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***Background*—**Excess adiposity, which affects 69% of US adults, increases coronary heart disease (CHD) risk in an association that manifests below conventional obesity cut points. The population-level impact on CHD risk that is attainable through modest adiposity reductions in populations is not well characterized. We estimated the effect of hypothetical reductions in both body mass index (BMI) and waist circumference (WC) on CHD incidence.

***Methods and Results*—**The study population included 13 610 ARIC (Atherosclerosis Risk in Communities) participants. Our hypothetical reduction in BMI or WC was applied relative to the temporal trend, with no hypothetical reduction among those with BMI >24 or WC >88 cm, respectively. This threshold for hypothetical reduction is near the clinical guidelines for excess adiposity. CHD risk differences compared the hypothetical reduction with no reduction. Sensitivity analysis was conducted to estimate the effect of applying the hypothetical BMI reduction at the established overweight cut point of 25. Cumulative 12-year CHD incidence with no intervention was 6.3% (95% CI, 5.9–6.8%). Risk differences following the hypothetical BMI and WC reductions were −0.6% (95% CI, −1.0% to −0.1%) and −1.0% (95% CI, −1.4% to −0.5%), respectively. These results were robust for the sensitivity analyses. Consequently, we estimated that this hypothetical reduction of 5% in BMI and WC, respectively, could have prevented 9% and 16%, respectively, of the CHD events occurring in this study population over 12 years, after adjustment for established CHD risk factors.

***Conclusions*—**Meaningful CHD risk reductions could derive from modest reductions in adiposity attainable through lifestyle modification. **(*J Am Heart Assoc*. 2020;9:e012214. DOI: 10.1161/JAHA.119.012214.)**

Key Words: body mass index • cardiovascular disease prevention • cardiovascular events • coronary heart disease • coronary heart disease risk

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Coronary heart disease (CHD) is the leading cause of death in the United States.[1–3] Although CHD mortality and incidence declined from 1987 to 2011,[4,5] a significant slowing in the average annual rate of decline was observed, which may reflect the burden of established risk factors for CHD such as obesity and diabetes mellitus.[6,7] In 2015, an estimated 69% of the US adult population was overweight and obese (body mass index [BMI] ≥25; calculated as kg/m^2),[8] and 9.4% had diabetes mellitus.[9]

A strong and continuous association has been observed between total adiposity and CHD,[10–12] and studies have evaluated the effect of reducing adiposity on CHD risk.[13,14] Several observational studies have reported an association between increased adiposity and increased risk of CHD,[15,16] whereas others have reported increased risk of CHD mortality following weight loss[17,18]; other studies focused mostly on total adiposity measured by BMI reported no association.[13,19,20] Lifestyle interventions to reduce obesity-associated CHD risk[21] focused largely on total adiposity indexed as BMI, but waist circumference (WC) is a surrogate measure

Clinical Perspective

What Is New?

- Estimation of the effect of a hypothetical reduction in body mass index and waist circumference on coronary heart disease risk in a cohort of black and white people.
- Stronger impact on the risk of coronary heart disease was observed for modification of waist circumference than body mass index.

What Are the Clinical Implications?

- These observational results suggest that modest reductions in adiposity measures in midlife have beneficial effects on the risk of coronary heart disease.
- Recommendations for achievable targets of waist circumference modification consistent with lifestyle modification may improve coronary heart disease risk.

for visceral adiposity,[22,23] which is associated with CHD even after adjusting for BMI.[24,25] Through its effects on metabolic dysregulation and vascular structure and function, visceral adiposity has an important role in assessing modification of CHD risk.[26] The national age-adjusted mean WC increased from 95.5 cm (95% CI, 94.2–96.8 cm) in 1999–2000 to 98.5 cm (95% CI, 97.5–99.4 cm) in 2011–2012.[27] In addition, the increase in the prevalence of elevated abdominal adiposity—46.4% (95% CI, 42.1–50.8%) in 1999–2000 to 54.2% (95% CI, 51.3–57%) in 2011–2012—was greater than expected based on increases in BMI,[5] possibly contributing to the observed slowing in the average annual rate of CHD decline. WC has a potential but understudied role in the assessment and modification of CHD risk[13,14] because WC is a reliable and feasible means of estimating central adiposity at the population level.[28,29]

Modifiable risk factors for CHD are well established, such as hypertension[30,31] and diabetes mellitus,[32–34] which together mediate much of the obesity-associated metabolic dysregulation that increases risk of CHD.[5,12,35–38] Because the effect of adiposity on CHD risk likely occurs through the well-documented adverse effects of excess adiposity on cardiometabolic intermediaries in the path to CHD, adiposity represents a modifiable, upstream risk factor for CHD.[12]

Previous reports have examined the effect on CHD of BMI interventions,[13,14] but little information is available examining the role of central adiposity, typically approximated by WC. In addition to evaluating WC, evidence is needed to evaluate the influence of modest intervention effects. We used the parametric g-formula because this approach can estimate the effect of interventions, such as reductions in modifiable risk factors such as BMI,[39] and overcomes some limitations of standard regression approaches.[40] Avoiding bias in this context requires consideration of time-dependent confounders that may be affected by the intervention.[41] To estimate the effect of reductions in adiposity, prior blood levels of, for example, lipoprotein lipids should be considered as a time-varying confounder, allowing for effects that reductions in adiposity may have on subsequent lipoprotein-lipid levels. Because the customary method of adding changes in both adiposity and lipoprotein-lipid levels as time-varying covariates in a regression model can lead to bias,[42] we used Robins g-formula[43] to estimate the effect of hypothetical interventions on the risk of incident CHD. The purpose of this study was to examine the effect of moderate hypothetical changes (5%) in total (BMI) and central (WC) adiposity on the incidence of CHD.

Methods

Availability of data and detailed policies for accessing ARIC (Atherosclerosis Risk in Communities) study data can be found online.[44] The ARIC study data are made available through the National Heart, Lung, and Blood Institute BioLINCC repository.[45]

Study Population

This study was conducted in the community-based, prospective, and predominantly black and white ARIC study cohort,[46] which includes 15 792 adults aged 45 to 64 years. ARIC cohort participants were recruited using probability sampling from 4 US communities: Forsyth County, North Carolina; Jackson, Mississippi; northwest suburbs of Minneapolis, Minnesota; and Washington County, Maryland. Only black residents were sampled in the Jackson study area.

Exclusions

Among the 15 792 ARIC participants who attended the first ARIC visit, we excluded those who reported a race other than black or white (n=48) and 55 black participants from Minnesota and Washington County because of small site-specific numbers. Also excluded were participants who reported morbidity or chronic conditions associated with weight gain or loss at baseline, including 871 with self-reported cancer, 79 taking heart failure medication, 19 with kidney failure (144 missing data on kidney function), and 667 with prevalent CHD. We excluded participants with missing data on baseline covariates and covariates related to exclusion criteria. For the analysis of the effect of a hypothetical shift in BMI, we excluded 58 participants missing information on BMI, smoking, hypertension, or diabetes mellitus and removed outliers by trimming observations of the baseline BMI distribution (n=241) above the race- and gender-specific 99th percentile of BMI (50.3, 43.5,

42.0, and 39.6 for black women, white women, black men, and white men, respectively) or lower than the 1st percentile (18.8, 18.1, 18.0, and 19.9, respectively) to arrive at our analytic set of 13 610 participants. For our analytic set of 13 301 participants for the WC analysis, we excluded 305 individuals missing information on WC, smoking, or BMI and trimmed observations below the race- and gender-specific 1st percentile and above the 99th percentile of the baseline distribution of WC. The 99th percentile of WC was 140, 130, 127, and 124 cm for black women, white women, black men, and white men, respectively, and the 1st percentile of WC was 70, 68, 99, and 99 cm, respectively.

Exposure, Covariate, and Outcome Ascertainment

Demographic and health characteristics were collected at the first examination during 1987–1989. Follow-up interviews were carried out approximately every 3 years for a total of 7 examination visits. Institutional review boards at each site approved the ARIC study, and all participants completed informed consent at each examination visit.[46,47] We limited our analysis to the first 4 triennial exams (1987–1999).

At each ARIC visit, standardized physical examinations and interviewer-administered questionnaires were used to gather behavioral information, medical data, and contextual data. All measurements taken at the ARIC examinations were collected by trained technicians following a common study protocol standardized across the repeated examination visits.[46] Annual follow-up telephone interviews ascertained health outcomes and hospitalizations.

Covariate information was ascertained during each of the 4 triennial study visits for BMI, WC (cm), cigarette smoking status (current compared with never and previous), hypertension (blood pressure >140/90 mm Hg or use of antihypertension medication within 2 weeks), and diabetes mellitus (fasting glucose ≥126 mg/dL, nonfasting glucose ≥200 mg/dL, diabetes mellitus medication use, or self-reported physician diagnosis).

Ascertainment of CHD events was conducted through annual telephone interviews of health events and hospitalizations and active surveillance of discharge lists from local hospitals and death certificates from state vital statistics offices. CHD events were validated by a morbidity and mortality classification committee. We defined incident CHD as the first occurrence of definite or probable hospitalized myocardial infarction, a definite CHD death, or an unrecognized myocardial infarction detected on 12-lead ECG.

Study participant follow-up extended until the first CHD event, CHD death, non-CHD death, or absence from an ARIC examination visit. If participants missed a study visit, they were considered to be at risk for incidence of CHD, CHD death, and non-CHD death for 3 years after that missed visit. For the purposes of this study, we administratively censored participants at 3 years after the fourth examination visit for consistent follow-up time throughout the ARIC study, as there are 3 years between each study visit. When our study was conducted, 3 years after visit 5 had not occurred.

Statistical Analysis

We estimated the risk of CHD under the specified interventions with the parametric g-formula,[14,39,40,43,48] a generalization of standardization for time-varying exposures and confounders.[41] Regression models were fit on the entire study population to predict each time-varying covariate, non-CHD death, and CHD. The fitted regression models were used to simulate CHD for each time period in each intervention, in the following sequence: use the observed covariate values at baseline, predict the joint distribution of the time-varying covariates at the next time point, set the values of the covariates to the values determined by the hypothetical intervention, predict the probability of CHD and non-CHD death using these new values, repeat all but the first step for each time period and estimate the population risk as the average of the subject-specific risks. Key assumptions of the parametric g-formula are that there is no residual confounding and no model misspecification.[14,39,40,43] The validity of the parametric models was assessed by comparing the observed means of the time-varying covariates risk of death and CHD with those predicted by the models. We used nonparametric bootstrapping with 200 samples to estimate the 95% CIs. We estimated the standard error to calculate the 95% CI as cumulative incidence $\pm 1.96 \times$SD (cumulative incidence) and risk difference $\pm 1.96 \times$SD (risk difference). Key assumptions of the parametric g-formula are that there is no residual confounding and no model misspecification. Another assumption is treatment version irrelevance, implying that the effect of a shift in BMI applied as a hypothetical change is the same as it would have been if it had occurred naturally.

Baseline covariates included in each of the regression models were race, sex, and education. CHD was included as annual incidence, and we used a carry-forward method to fill in the covariates between the approximately triennial ARIC study visits for WC, BMI, diabetes mellitus, hypertension, and smoking status. Time-varying covariates included in each of the regression models were years at risk for CHD, diabetes mellitus, hypertension, smoking, and measure of adiposity specific to each analysis of a hypothetical 5% reduction in total (BMI) or central (WC) adiposity.

For the BMI and WC analysis, we resampled with replacement for 1 360 000 and 1 330 000 "pseudo-participants," respectively. No hypothetical adiposity reduction was applied to this simulated data set, which is identified as the "natural course." We applied a 5% reduction in BMI relative to the

trajectory of BMI from the natural course within the population who were aged <65 years and had BMI >24 (for the BMI analysis) or WC >88 (for the WC analysis). The cumulative incidence of CHD was estimated while allowing for competing risks from death or censoring.[49] All analyses were conducted using SAS 9.4 (SAS Institute). As a sensitivity analysis, we estimated the effect of applying the hypothetical BMI reduction at the established BMI cut point for overweight of BMI 25.

Results

Characteristics of Study Participants

Over ≈12 years of follow-up, 763 and 712 incident CHD events occurred among the 13 610 (BMI analysis) and 13 301 (WC analysis) middle-aged participants, respectively, in this cohort. Participants with incident CHD were more likely to be male, to be white, and to have less than a high school education compared with those without incident CHD. Smoking, diabetes mellitus, and hypertension were more frequent at baseline among those who developed incident CHD compared with those without incident CHD. Participants who did not develop incident CHD had more favorable cardiometabolic risk profiles compared with those who developed incident CHD (Table 1).

The median BMI was between 26.9 and 28.2 in the natural course and between 24.7 and 25.6 in the population in which a hypothetical 5% shift in BMI was applied to those with a BMI >24 who were aged<65 years. The median WC was between 95.9 and 100.6 cm in the natural course and between 88.6 and 93.8 cm in the population exposed to a hypothetical 5% shift in WC. For the BMI analysis, the cumulative incidence of CHD under the natural course was 6.3% (95% CI, 5.9–6.8%) and 5.8% (95% CI, 5.2–6.4%) following the hypothetical BMI change. The risk difference was −0.6% (95% CI, −1.0% to −0.1%) comparing no BMI change with the hypothetical BMI change (Table 2). For the WC analysis, the cumulative incidence of CHD, which started to diverge at around 5 years of follow-up in the natural course, was 6.2% (95% CI, 5.8–6.7%) and 5.2% (95% CI, 4.6–5.9%) following the hypothetical WC change. The risk difference was −1.0% (95% CI, −1.4% to −0.5%) comparing the hypothetical WC change with no WC change (Table 2). Consequently, we estimated that this hypothetical reduction of 5% in BMI and WC, respectively, after adjustment for race, sex, education, diabetes mellitus, hypertension, and smoking, could have prevented 9% and 16% of the CHD events occurring in this study population over 12 years.

Discussion

Our results indicate that plausible and meaningful reductions in CHD risk could be achieved by modest reductions in total (BMI) and central (WC) adiposity over the course of 12 years, relative to the observed temporal trends. Reduction in CHD risk was larger with a hypothetical WC reduction compared with BMI reduction. Our hypothetical reductions in adiposity were consistent with the clinically recommended weight reductions of 5% to 10% for people who are overweight.[50] We applied a hypothetical shift to the population distribution of adiposity at a threshold that was established to be near the clinical guidelines for excess adiposity; for the ARIC population, this was at the 24th percentile of the baseline distribution of BMI and WC. Unlike BMI, WC does not have well-established clinical guidelines for excess adiposity; therefore, we used an equivalent threshold for WC by applying a hypothetical shift at the 24th percentile of the WC distribution, which corresponded to 88 cm.

The larger risk reduction in CHD following a hypothetical WC reduction compared with a hypothetical BMI reduction suggests a stronger metabolic impact of WC modifications and the associated risk of CHD.[22–24] We considered that this larger risk reduction following a hypothetical WC reduction compared with a BMI reduction could be related to residual confounding if preclinical disease is present[51]; however, we adjusted for morbidity and chronic conditions at baseline that were related to weight change.[13]

Other studies have demonstrated associations between abdominal adiposity and CHD independent of BMI.[52–55] Furthermore, genetic evidence supports a causal association between abdominal adiposity and development of CHD.[56] WC was a better predictor of risk for developing diabetes mellitus than other anthropometric measures in the DPP (Diabetes Prevention Program).[57] Comparing our findings with those of large clinical trials such as the DPP, the 5% reduction we applied to WC (4.4–5.5 cm) is similar to the 4-cm WC reduction observed in the DPP, which was associated with a 24% reduction in risk of diabetes mellitus over 10 years of follow-up among participants who were randomized to an intensive lifestyle intervention.[58]

The effect of modest hypothetical shifts in the population distribution of BMI on incidence of CHD was examined[13,14] using data from the Nurse's Health Study. The authors modeled several hypothetical lifestyle interventions,[14] one of which was targeted maintenance of BMI <25; the authors did not observe this intervention having an effect on the incidence of CHD. Because this BMI reduction over the 2-year time period was unrealistic, the authors proposed (but did not test) a hypothetical intervention that would reduce BMI by a small percentage (ie, 5%), which is similar to the hypothetical intervention that we implemented.

A focus on central adiposity also opens opportunities for public health messages that address modification in WC or perhaps clothing size as a more tangible measure than ratio formulation such as BMI. Moderate-intensity exercise is

Table 1. Characteristics of the Study Population at Baseline by Incidence of CHD

Characteristic	Incident CHD		Without Incident CHD	
	BMI Analysis, n=763	WC Analysis, n=712	BMI Analysis, n=12 847	WC Analysis, n=12 589
Female	254 (33)	230 (32)	7356 (57)	7208 (57)
Black	207 (27)	190 (27)	3490 (47)	3419 (27)
Less than HS graduate	230 (30)	211 (30)	2892 (23)	2828 (23)
HS graduate or vocational school	291 (38)	270 (38)	5258 (41)	5162 (41)
Some college or college graduate	241 (32)	230 (32)	4681 (36)	4583 (36)
Current smoking	221 (29)	285 (40)	2032 (16)	3423 (27)
Diabetes mellitus	213 (28)	242 (34)	1867 (15)	2402 (19)
Hypertension	450 (59)	487 (68)	5995 (47)	7106 (57)
Follow-up, y	6.0 (3.0–8.8)	5.8 (3.0–8.6)	11.8 (9.0–11.9)	11.8 (9.1–11.9)
Age, y	62 (57–66)	62 (56–66)	54 (49–59)	63 (59–68)
BMI, kg/m^2	27.8 (25.1–31.0)	NA	26.8 (24.0–30.3)	NA
WC, cm	NA	102 (94–99)	NA	100 (92–99)
SBP, mm Hg	126 (115–140)*	126 (115–140)	118 (108–130)†	118 (108–130)
FPG, mg/dL	104.0 (95–122.3)	104.0 (95–122.3)	99.0 (92.4–106.9)	99 (92.4–107)
TC, mg/dL	221 (195–248)‡	222 (196–249)	212 (186–239)§	212 (186–239)
HDL-C	41.4 (34.7–51.0)‖	41 (34–51)	50.0 (40.4–61.6)¶	49.1 (40.4–61.6)

Data are from the ARIC (Atherosclerosis Risk in Communities) study (1987–1999) and are shown as n (%) or median (interquartile range). BMI analysis: n=13 610; WC analysis: n=13 301. Diabetes mellitus was defined as fasting glucose ≥126 mg/dL, nonfasting glucose ≥200 mg/dL, diabetes medication use, or self-reported physician diagnosis. Hypertension was defined as blood pressure >140/90 mm Hg or use of antihypertension medication within 2 weeks. BMI indicates body mass index; CHD, coronary heart disease; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HS, high school; NA, not available; SBP, systolic blood pressure; TC, total cholesterol; WC, waist circumference.
*n=762.
†n=12 842.
‡n=757.
§n=12 756.
‖n=758.
¶n=12 757.

associated with significant reductions in total fat, visceral fat, and skeletal muscle lipid content.[59] Increased cardiometabolic fitness is associated with reduction in mortality and morbidity independent of BMI.[60] Such an approach that targets central adiposity may also encourage those who appear resistant to substantial weight loss despite considerable effort.

Population-based programs aim to achieve sustained effects of modest magnitude, but wide penetration is needed to complement clinical efforts that target excess adiposity and to influence cultural norms and trends that shift adiposity levels in populations.[11,61–64] Waist girth and central adiposity tap into cultural norms and popular perceptions different from

Table 2. Estimated Cumulative 12-Year Incidence and Risk Difference of CHD for the Natural Course Cohort Compared With the Cohort With a Hypothetical 5% Shift in the Population Distribution of Adiposity

Cohort*	Measure of Effect	Estimate (%)†	95% CI
Natural course for BMI	Incidence	6.3	5.9–6.8
Hypothetical 5% BMI reduction	Incidence	5.8	5.2–6.4
Natural course vs hypothetical reduction	Risk difference	−0.6	−1.0 to −0.1
Natural course for WC	Incidence	6.2	5.8–6.7
Hypothetical 5% reduction in WC if WC >88 cm	Incidence	5.2	4.6–5.9
Natural course vs hypothetical WC reduction	Risk difference	−1.0	−1.4 to −0.5

Data are from the ARIC (Atherosclerosis Risk in Communities) study (1987–1999). BMI indicates body mass index; CHD, coronary heart disease; WC, waist circumference.
*For the BMI and WC analyses, there were 763 and 712 CHD events among 13 610 and 13 301 ARIC participants, respectively, after 12 years of follow-up.
†Baseline covariates included in the models were age, sex, race, and education. Time-varying covariates included in the models were years at risk for CHD, diabetes mellitus, hypertension, smoking, and measure of adiposity specific to each analysis of a hypothetical 5% reduction in total (BMI) or central (WC) adiposity.

those surrounding BMI and total adiposity,[65,66] as reflected in messages in the media and health-product outlets. Our results warrant replication in other population-based longitudinal studies with access to cultural, racial/ethnic, and socioeconomic diversity. These results also suggest the need for assessments of the relative merit of hypothetical shifts in WC and BMI distributions for other health outcomes influenced by adiposity and more closely linked causally and temporally to adiposity than is the case for CHD.

Our analyses were limited to the initial 4 visits of the ARIC cohort; as a result, the length of our follow-up likely did not fully capture the long-term impact of adiposity at midlife on the risk of CHD during the life epochs when the incidence of CHD is highest. Because the use of WC as a measure of adiposity is reportedly not accurate in people with a BMI >40,[50] we excluded participants at the upper and lower 1% of the baseline population distribution of WC; this was also done for the BMI analysis. Consequently, our estimates are not generalizable to the excluded segment of the population. The strengths of our study derive from estimation of the effect of a hypothetical reduction in BMI and WC on the incidence of CHD in a cohort of black and white men and women, to our knowledge, for the first time. This report adds new information to the literature on the effects of hypothetical shifts in total and central adiposity on the incidence of CHD in a middle-aged black and white cohort. Declines in mortality and incidence of CHD have been reported over the past decade, and ongoing primary prevention of risk factors for CHD would be required to continue the trajectory of these declines.[67]

The population distribution of adiposity is dynamic and subject to diverse influences[11,68,69] and temporal trends.[6,7] Desirable shifts in population distributions of adiposity are the focus of public health policies aimed at serving sizes, limits on sugar-sweetened beverages,[70–72] subsidies for healthier food choices, and increased accessibility for physical activity, among others. Using CHD as a sentinel condition, our results estimate a modest effect on the incidence of CHD following moderate, population-wide shifts in central adiposity and, to a lesser degree, total adiposity. Although traditionally focused on total adiposity, clinical and public health recommendations that promote health and longevity should consider achievable targets for WC modification, perhaps through lifestyle modification.

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Disclosures

None.

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