Most Important Outcomes Research Papers on Body Weight, Obesity and Cardiovascular Outcomes

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The following are highlights from the new series, Circulation: Cardiovascular Quality and Outcomes Topic Review. This series will summarize the most important manuscripts, as selected by the Editor, that have published in the Circulation portfolio. The objective of this new series is to provide our readership with a timely, comprehensive selection of important papers that are relevant to the quality and outcomes, and general cardiology audience. The studies included in this article represent the most significant research related to body weight and obesity. (Circ Cardiovasc Qual Outcomes. 2013;6:e48-e56.)

Body weight, and its extreme of obesity, has emerged as a major public health concern. Nearly 1/3 of the adult US population is now estimated to be obese, as defined by a body mass index (BMI), the weight in kilograms divided by the square of the height in meters) ≥ 30.1 The cost of obesity on the healthcare system is substantial; an estimated $147 billion in medical costs were attributed to obesity alone in US in 2008.2 Furthermore, the prevalence of childhood and adolescent obesity, which now affects 17% of children and adolescents,1 raises concerns for its impact on adulthood obesity and long-term health outcomes. In this month’s topic review in Circulation: Cardiovascular Quality and Outcomes, we concentrate on contemporary issues around body weight, obesity, and cardiovascular outcomes.

Many hurdles remain in evaluating the relationship between body weight and cardiovascular (CV) outcomes. Debate continues as to the optimal measure of adiposity; body mass composition, and specifically excess adiposity, is perhaps a more appropriate marker of cardiovascular risk compared to body weight. BMI, although widely used, is an imperfect measure of excess adiposity with evidence favoring central obesity, as measured by the waist circumference, as a more sensitive indicator of adverse long-term cardiovascular events.3 Moreover, the effects of obesity on cardiovascular outcomes are complex. Studies have suggested that patients with higher BMIs had better survival compared with those with low BMIs; a phenomenon frequently referred to as the obesity-risk paradox.4 Obesity itself is often associated with multitude of other cardiovascular risk factors such as hyperlipidemia, diabetes, and hypertension; untangling the independent effects of obesity on outcomes thus remains challenging. Lastly, while evidence now suggests obesity is an independent risk factor for long-term adverse cardiovascular events, weight reduction remains an extremely challenging exercise for obese patients. Furthermore, no randomized data has shown that weight reduction improves cardiovascular mortality. However, even modest weight loss in obese patients is associated with an improvement in risk factor profile,5 a finding which forms the basis of current guidelines and recommendations for maintaining an ideal body weight.

We focus on these challenges in the following topic review for Circulation: Cardiovascular Quality and Outcomes. For this topic review, we performed a rigorous literature search of all contemporary articles published in the Circulation portfolio of journals on PubMed, searching for ‘body weight’, ‘obesity’, ‘underweight’, ‘overweight’, ‘weight’, ‘body mass index’, and all their variations as search terms and MeSH keywords, and then at least 3 authors manually reviewed each article for appropriateness for inclusion. We have included papers that evaluate (1) the epidemiology of body weight and obesity, (2) the relationship between body weight and cardiovascular disease, and (3) the effects of environmental, genetic, and other factors on body weight and obesity.

Epidemiology of Body Weight and Obesity

Now, more than ever, it is important to recognize and understand body weight as a key modifiable behavioral risk factor for modern cardiovascular disease (CVD). Modifiable risk factors are known to be the leading cause of mortality in the US.6 Studies have shown that changes in body weight accounted for nearly 150,000 excess deaths in 2000, the vast majority of which were due to obesity.7 Being underweight slightly increased mortality from non-cancer and non-CVD causes, overweight decreased all-cause mortality, while obesity significantly increased CVD mortality and had the largest effect on overall excess deaths.8 Since then, the prevalence of obesity has increased in the US among men, non-Hispanic black women, and Mexican American women, resulting in an overall obesity rate of 36% among both adult men and women in 2009–2010.9

To improve this growing problem, it is important to understand the epidemiology, prevalence, and trends in contemporary body weights. The American Heart Association has published the 2020 Strategic Impact Goals setting an improvement in CV risk factors by 20%, which may lead to 24% decrease in CV mortality.10 However, before we can attain such goals, it is necessary to elucidate the current prevalence of body weights across various populations. The studies here investigate the current epidemiology of body weight and CV risk factors, both nationally and internationally, along with how they are changing over time.12–14

Cardiovascular Health Behavior and Health Factor Changes (1988–2008) and Projections to 2020: Results From the National Health and Nutrition Examination Surveys

Summary: The American Heart Association’s 2020 Strategic Impact Goals target a 20% improvement in overall cardiovascular health in all Americans, but there are few studies describing current trends in
CV health metrics and whether such targets would be attainable. The authors used the Third National Health and Nutrition Examination Surveys (NHANES III, 1988–1994) and subsequent 2-year NHANES cycles up to 2008 to define trends and forward projections to 2020 in CV health behaviors and factors. Time trends were estimated using weighted linear regression, adjusted for age, and projections were calculated assuming that trends would continue at a similar linear rate. Data from 35,059 NHANES CV disease-free participants aged ≥20 years (mean age: 44.4 years; 51% women) showed substantial increases in obesity (from 20% in 1988 to 32% in 2008) and poor or intermediate levels of glucose/diabetes control (from 21.1% to 42.9%). However, the poor behaviors/factors of smoking and hypercholesterolemia across both genders along with lack of physical activity and hypertension in men all improved from 1998–2008. Projections to 2020 suggest that obesity may reach 43% while the prevalence of diabetes will increase to 14% in men and 8% in women, with less than half of women and a quarter of men having ideal glucose levels. Projected improvements of 20% will be met for smoking, physical activity, blood pressure, and cholesterol. However, the composite of all factors measuring overall CV health is projected to improve by only 6.04%, short of the AHA target of 20%.

Conclusions: This study suggests that CV health from 1988–2008 show worsening trends in body weight, obesity, diabetes, and glucose control, along with concomitant improvements in smoking, cholesterol, physical activity, and hypertension. Projections show the US falling far short of the target of 20% improvement in CV health, which carries with it a projected 24% decrease in coronary heart disease deaths, with the caveat that this model assumed a continuation of linear trends. However, a separate projection of trends to 2020 arrived at a similar result of decreased smoking and increased BMI, with further analysis concluding that any improvements in life expectancy from less smoking would be overwhelmed by negative effects of increasing obesity. Based on such results, it is clear that obesity is one of the most important public health challenges in the modern era and drastic changes may be needed if we are to improve such grim projections.


Summary: The American Heart Association’s Strategic Impact Goals for 2020 lists numerous criteria for ideal CV health, including CV disease, health behaviors, and health factors, but little is known of such metrics based on age, sex, and race/ethnicity. The authors used data from the 2003–2008 NHANES, collected in 2-year cycles. Participants (n=14,515 participants) were stratified by age into 3 age groups: young (20–39 years), middle age (40–64 years) and older age (≥65 years), and by sex, race/ethnicity, educational level, and household income. The study found that nonsmoking was the most prevalent healthy behavior across groups (60–90%), while healthy diet score was the least prevalent (0.2–2.6%). For body weight, ≥50% of young adults and ≥67% of middle-aged and older adults had non-ideal BMIs of ≥25. Across ethnicities, non-Hispanic white women and Mexican-American men had the highest prevalence of being overweight or obese (BMI ≥25) while non-Hispanic white women had the lowest prevalence. Overall, <1% of all adults exhibited the ideal levels of all 7 CV health components. Number of health components met was generally lower in older age groups, and in men. The distribution was similar across race/ethnicity when examined by age groups.

Conclusions: The study results demonstrate a baseline for monitoring CV health in the general US population as we strive toward the goals for 2020. Since so few participants demonstrated ideal CV health, it may be difficult to achieve this goal for large proportions of the US population. However, given the high proportions of overweight or obese participants across all groups, body weight plays a large role in the unfavorable state of CV health in the US and represents a potential major target for improvement in efforts to attain these goals. The differences across age and racial/ethnic groups suggest that customized interventions targeted for each high-risk group may be needed to effectively combat this major public health problem.


Summary: Cardiovascular risk factors, such as excess body weight (as reflected by BMI), are often assumed to be associated with Westernized diet (WD) and higher socio-economic status. In this study, the authors conducted population level analyses to examine whether BMI was associated with national income (as measure by Gross Domestic Product (GDP) in SUS), WD, and urbanization in 1980 and 2008. In addition, they evaluated whether fasting plasma glucose (FPG), systolic blood pressure (SBP), and serum total cholesterol (TC) correlate with national income and a WD. Mean BMI, FPG, SBP, and TC in 1980 and 2008 were derived from a systematic analysis of population-based data, by sex, for 190 countries and territories, as described in prior studies. The results show that in 1980, population mean BMI (along with SBP and TC) were positively associated with national income among women but not men. The correlation coefficients for BMI ranged between 0.34 and 0.50 with the slope for BMI over income in women flattening out as the national income exceeded $7000. By 2008, the relationship between GDP and BMI resembled an inverted U for women, peaking at middle-income levels. In contrast, among men, BMI was correlated with WD in 1980 with a linear increase in BMI with increased adoption of WD. A weaker relationship between BMI and WD among men was noted in 2008. Mean BMI was positively associated with urbanization in both 1980 and 2008, with slopes ranging between 0.54 and 0.7 kg/m² per 10-percentage point increase in urbanization. Only TC (but not SBP or FG) remained strongly positively correlated with national income and WD in 2008.

Conclusions: This study suggests that the relationship between obesity and population income and a WD is both complex and dynamic. The authors propose that increased caloric intake from traditional sources among low- and middle-income countries, as opposed to a WD alone, may explain the weakening relationship between BMI and WD with time. Furthermore, these data suggest urbanization may be independently associated with BMI irrespective of household income or WD, which may reflect the role of physical inactivity in urban populations. However, these data must be interpreted with caution; conclusions drawn from national level summary data may not be applicable at the level of individual persons.

Relationship Between Body Weight and Cardiovascular Disease

High body weights have been implicated in increasing cardiovascular risk through the parallel rise noted in rates of obesity and cardiac disease in recent decades. Besides being an independent moderator of cardiac risk, obesity also promotes a cascade of secondary pathologies including diabetes and insulin resistance, dyslipidemia, inflammation, thrombosis, hypertension, the metabolic syndrome, and obstructive sleep apnea, which collectively heighten the risk for cardiovascular disease. Recent evidence has linked obesity to intrinsic cardiac conditions including coronary artery disease (CAD), heart failure (HF), cardiomyopathy, and atrial fibrillation (AF). Moreover, excess adiposity appears to amplify the risk of actual coronary events than those predicted by Framingham CHD risk scores in patients who are followed over time.

Despite the fact that obesity is tightly linked with increased cardiovascular risk, its effect on clinical outcomes is more complex, thus leading to the emergence of the concept of the ‘obesity outcome
paradox”. Recent evidence has indicated that overweight/obese patients with established cardiac disease have either improved survival or no worsening of outcomes as compared with patients with normal BMI. Such a relationship has been demonstrated for HF, hypertension, CAD, and in those who undergo coronary revascularization procedures including CABG and PCI. The mechanism underlying this ‘survival paradox’ remains unclear.

Given that body weight is potentially one of the most preventable and remediable mediators of cardiovascular disease, effective interventions may have a favorable impact on public health. The following summaries concern multiple topics pertinent to the effect of obesity on cardiovascular disease risk and outcomes for conditions including HF, CAD, outcomes after PCI, venous thromboembolism, metabolic syndrome, hypertension and diabetes.

**Association of Body Mass Index With Major Cardiovascular Events and With Mortality After Percutaneous Coronary Intervention**

**Summary:** The association between BMI, cardiac events and death following percutaneous coronary intervention (PCI) is unclear. However, studies have suggested that obese individuals have a better prognosis than normal or lower BMI groups, an observation known as the ‘obesity paradox’. To answer these questions the authors examined the relationship between BMI, risk of major cardiovascular events (MCE) and mortality following PCI. Data was pooled from 11 prospective South Korean studies with a total of N=23,181 participants (30% women). Patients with no BMI data, cardiogenic shock, terminal illness, or malignancy at baseline were excluded. MCEs were defined as the composite of death from cardiovascular causes, nonfatal myocardial infarction, stent thrombosis, or stroke. BMI was divided into 2.5 unit increments from <18.5 to ≥30.0. Cox proportional hazards models were utilized to discern the association between BMI and the risks of MCE/death. In the pooled population, the mean BMI was 24.9±3.0, and patients had 2381 MCE and 1004 deaths over a 2.1 year median follow-up. In both the unadjusted and adjusted analyses, there was a significant inverse relationship amongst BMI and adverse outcomes, with higher BMIs associated with a lower risk of MCE. Compared with the reference BMI of 22.5–24.9, the risk of MCE was elevated in those with a lower BMI (hazard ratio [HR]:1.52 for BMI<18.5; 1.05 for BMI of 18.5–19.9; 1.03 for BMI of 20.0–22.4) and lower among participants with a higher BMI (HR: 0.97 for BMI of 25.0–27.4; 0.97 for BMI of 27.5–29.9; 0.78 for a BMI of ≥30.0). Across the board, hazard ratios for all-cause mortality, suggesting that obesity may be protective or harmless for cardiovascular risk amongst those patients receiving PCI. This finding may be important for developing future risk stratification for this important population. However, this study has some important limitations, including uncertainty over how the 11 prospective studies were chosen (i.e. each study was designed to report different factors), heterogeneity of the samples or study designs, the potential lack of generalizability to other ethnic cohorts and the lack of body composition/body fat distribution data, which may have provided more clues on the link between adiposity-related outcomes.

**Body Mass Index and Adverse Cardiovascular Outcomes in Heart Failure Patients With Preserved Ejection Fraction: Results From the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) Trial**

**Summary:** Heart failure patients with a higher BMI tend to have a better prognosis compared to patients with a lower BMI. Using data from the Irbesartan in HF with Preserved Ejection Fraction (I-PRESERVE) randomized control trial, the relationship between BMI and the primary composite outcome of death or cardiovascular hospitalization in patients with preserved EF was examined. The study consisted of 4109 patients (mean age 72 years) and with a mean follow up period of 49.5 months. Based on the BMI distribution, five BMI categories were defined: ≤23.5, 23.5 to 26.4, 26.5 to 30.9, 31 to 34.9, and ≥35. Most patients (71%) had a BMI ≤26.5, 21% had a BMI between 23.5 and 26.4, and 8% had a BMI ≥23.5. Patients with higher BMI were younger, more likely to be women, and more likely to have comorbidities such as hypertension and diabetes Finally, patients with higher BMI had increased use of angiotensin converting enzyme inhibitors, beta-blockers, calcium channel blocking and lipid-lowering agents. Patients with BMI of 26.5 to 30.9 had the lowest rate of the primary composite outcome (35.1% rate of death or cardiovascular hospitalization) and were used as reference group. After adjustment for 21 risk variables known to independently affect the primary outcome, the hazard ratio for the primary outcome was increased in patients with BMI ≤23.5 (HR: 1.27; 95% Confidence Interval [CI] 1.04 to 1.56; P=0.019) and in those with BMI ≥23 (HR: 1.27; 95% CI: 1.06 to 1.52; P=0.011) compared with the reference group. A similar relationship was found for secondary outcomes such as all-cause mortality and for HF hospitalization.

**Conclusions:** The present study extends current literature by demonstrating the presence of an “obesity paradox” in patients with HF with preserved ejection fraction (EF). Prior studies have shown a linear relationship with worsening outcomes with decreasing BMI. However, these studies have generally grouped patients with BMI greater ≥30. In contrast, by further categorizing patients with high BMIs, the authors demonstrated that the relationship between BMI and outcomes is not linear and severe obesity (BMI ≥35) might portend a poor prognosis as well. Multiple explanations including increased metabolic reserve, decreased levels of prognostic biochemical markers such NT pro-BNP as well as an independent, cardioprotective role of adipose tissue could possibly explain the beneficial effect of moderate increase in BMI on cardiovascular health and outcomes. However, the present study suggests that both a low BMI and extremely high BMI are associated with adverse outcomes in HF patients with preserved EF.

**Childhood Physical, Environmental, and Genetic Predictors of Adult Hypertension: The Cardiovascular Risk in Young Finns Study**

**Summary:** Hypertension is a major cardiovascular risk factor, and prior studies have raised the possibility that factor such as parental hypertension and childhood obesity may impact the development of adult hypertension. However, the independent impact of childhood genetic, physical, and environmental factors, including childhood body weight and obesity, on the risk of adult hypertension is less well known. The authors examine this question using a study cohort which included 2625 individuals from the Cardiovascular Risk in Young Finns Study with 21 to 27 year follow-up from 1980 (mean age at enrollment 3–18 years). The impact of genetic markers, parental factors including parental hypertension, childhood physical characteristics including overweight/obese status, dietary factors, and biomarkers related to blood pressure were evaluated. The primary outcome was incident hypertension in adulthood, defined as systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg or medication for the condition. Univariate analysis showed that childhood overweight/obesity status (OR 2.18; 95%CI 1.62–2.93) and childhood pre-hypertension (OR 2.18; 95%CI 1.82–2.61) were the strongest predictors of adult hypertension. In the multivariable analysis, childhood overweight/obese status continued to be a strong predictor of adult hypertension (OR 1.65, 95%CI 1.16–2.34). In addition, parental hypertension, elevated childhood systolic blood pressure, and genetic markers of hypertension increased the risk of adult hypertension.
**Conclusions:** Hypertension is a major modifiable risk factor for cardiovascular disease in later life. This longitudinal study suggests being overweight or obese during childhood has a significant adverse influence on the risk of developing adult hypertension, irrespective of other risk factors including genetic markers and parental hypertension. Among adults, weight reduction is known to lower SBP and reduce the risk of developing hypertension. Whether weight reduction among overweight or obese children is a beneficial intervention for reducing hypertension, and the long-term risk of CV events, is unknown. Nevertheless, this study adds to a growing body of evidence that suggests childhood obesity is a serious public health issue with a clear detrimental effect on long-term health outcomes.

**Body Mass Index and Risk of Incident Hypertension over the Life Course: The Johns Hopkins Precursors Study**

**Summary:** While the prevalence of hypertension and obesity is increasing globally, the link between obesity and hypertension over the life course has not been well characterized. The authors sought to fill this gap by studying the association of BMI in young adulthood (measured at 25 years of age) and middle age (measured at 45 years of age) with the risk of developing hypertension in later life in 1132 white men from the Johns Hopkins Precursors Study, a prospective cohort study. They found that, over a median follow-up of 46 years, obesity (BMI ≥ 30) in young adulthood was strongly associated with incident hypertension (HR 4.17; 95% Cl. 2.34–7.42). In addition, being overweight (BMI 25 to <30) also showed an increased risk of latter incidence of hypertension (HR 1.58; 95% Cl. 1.28–1.96). After adjusting for multiple time-dependent factors, such as number of cigarettes smoked, alcohol intake, baseline BMI, and physical activity, the rate of change in BMI over the life course increased the risk of incident hypertension in a dose-response manner, with the highest risk among men with the greatest BMI increase (HR 2.52; 95% Cl. 1.82–3.49).

**Conclusions:** This study effectively illustrates the important relationship of higher body weight and weight gain with increased lifetime risk of hypertension. The results are notably limited to only white men, as it was derived from a study initiated in 1947, addressing neither gender and racial differences nor how a more modern diet with the influx of processed foods and access to fast foods may affect weight gain and hypertension. However, this understanding of the association between obesity and hypertension over the life course is instrumental to understanding the problem of increasing hypertension and knowing where and when to implement changes to reverse this trend. More specifically, it suggests that body weight and weight gain early in life have a major effect on long-term outcomes. Therefore, early intervention for obesity may be a strong leverage point to maximize the reduction in lifetime risk for hypertension.

**The Effect of Excess Weight Gain with Intensive Diabetes Treatment on Cardiovascular Disease Risk Factors and Atherosclerosis in Type 1 Diabetes: Results From the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC) Study**

**Summary:** Intensive insulin therapy for type 1 diabetes mellitus (T1DM) reduces complications, but may lead to weight gain, central obesity, and dyslipidemia. How these factors contribute to the risk of long-term atherosclerotic disease is uncertain. The 1983 Diabetes Control and Complications Trial (DCCT) assessed intensive vs. conventional insulin therapy over a 6.5 year period. These patients were then followed-up in the Epidemiology of Diabetes Interventions and Complications (EDIC) study for >17 years. Using data from these studies, the authors assessed whether patients who gain the most weight during the DCCT study had worse markers of atherosclerotic disease (carotid intima media thickness (IMT) and coronary artery calcium (CAC) score), and evidence of the metabolic syndrome (hyperlipidemia, hypertension, and central obesity as measured by waist circumference [WC]). Excess weight gainers were those who were in the highest quartile of BMI change, defined as increases of at least 4.39 kg/m² in the intensive arm and 2.24 kg/m² in the conventional arm. The results showed that excess weight gainers continued to have greater BMI and WC at follow-up, required more insulin, had greater IMT (+5%, P<0.001 EDIC year 1, P=0.003 EDIC year 6), and trended towards greater CAC scores (OR 1.55, CI 0.97–2.49, P=0.07) compared to the rest of the study participants. Excess weight gainers also had higher lipid levels, higher systolic and diastolic blood pressure, greater use of lipid lowering and anti-hypertensive medications, and were more likely to meet the criteria for metabolic syndrome at long-term follow-up. Lastly, among excess weight gainers, these adverse markers of cardiovascular risk were more likely to occur among patients who were treated with intensive insulin therapy compared to those treated with conventional insulin regime.

**Conclusions:** This study suggests that intensive insulin therapy is associated with weight gain in some patients such that these patients begin to develop characteristics of central obesity and the metabolic syndrome, more often associated with type 2 diabetes mellitus. This raises the question of whether a less stringent insulin regime should be used in T1DM patients who gain weight with insulin therapy. However, these results must be interpreted with caution. IMT and CAC score are surrogate markers of adverse cardiovascular outcomes. Indeed, the long-term follow-up of the DCCT cohort has previously shown an overall reduction in incident chronic kidney disease, a 42% reduction in cardiovascular events (P=0.02), and a 57% reduction in the risk of nonfatal myocardial infarction and stroke (P=0.02) in the intensive therapy arm, indicating an overall beneficial effect of tight glycemic control in patients who tolerated therapy.

**Cardiorespiratory Fitness, Body Mass Index, and Heart Failure Mortality in Men: Cooper Center Longitudinal Study**

**Summary:** The obesity epidemic, caused in part by physical inactivity, is highly prevalent in the United States, but there is limited data on the effects of cardiorespiratory fitness (CRF) and BMI on heart failure. Therefore, this longitudinal study assessed associations among BMI, CRF and HF mortality in fit versus unfit men (fit defined as >80th percentile of CRF). Data from 1971–2010 was utilized from the Cooper Center Longitudinal Study, which included N=44,674 men free of prior CV disease, with a BMI ≥18.5 and ≥1 year of follow-up. At baseline, men were classified as either normal weight (BMI 18.5–24.9), overweight (BMI 25.0–29.9) or obese (BMI 30) and CRF was computed as the standardized performance of maximal graded treadmill testing. Mortality data was extracted from the National Death Index. Cox proportional hazards models were used to compute hazard ratios for each CRF and BMI category. The mean follow up time was 19.8±10.4 years with 153 HF deaths. Those deceased from HF had more comorbidities/CV risk factors, a higher BMI and lower CRF than survivors. There was a significant increasing trend in HF mortality across decreasing CRF categories (HR for high, moderate and low CRF: 1.0, 1.63 and 3.97, respectively) and across increasing BMI categories (HR for normal, overweight and obese: 1.0, 1.56 and 3.71 respectively), which persisted after adjustment. Moreover, when grouped into fit and unfit categories, HRs were found to be significantly lower in fit versus unfit men in normal and overweight categories, but not in obese men. Lastly, fit men had a significantly lower HF mortality in comparison to unfit men.

**Conclusions:** This study of healthy men suggests that a lower BMI or higher CRF is each correlated with a reduction in HF mortality,
independent of other cardiac risk factors present. Furthermore, the measurement of both combined BMI and CRF seem to be advantageous over BMI alone in determining risk of future HF mortality. It is important to note that this study was limited to healthy Caucasian men largely from upper socioeconomic backgrounds and thus these findings may not be generalizable to women or other cohorts. Despite this, the study sheds important insight into potential mechanisms to decrease HF mortality in men through losing weight and increasing levels of physical activity.46

**Long-Term Effects of Changes in Cardiorespiratory Fitness and Body Mass Index on All-Cause and Cardiovascular Disease Mortality in Men: the Aerobics Center Longitudinal Study**

**Summary:** Many experts recommend weight loss or exercise for improving the cardiovascular health and longevity.47 However, insufficient data exist about the association between changes in cardiorespiratory fitness, BMI, and mortality. Using the data from the Aerobics Center Longitudinal Study, a prospective observational study in the United States, the authors determined such associations among 14,345 men. Cardiorespiratory fitness was estimated by a maximal treadmill test and changes in fitness (loss, stable, gain) were determined between the follow-up visits, as was the change in BMI (loss, stable, gain based on BMI). Over an 11.4 year follow-up period, there were 914 deaths, 300 of whom were due to cardiovascular causes. Compared with fitness loss, stable fitness and improved fitness were associated with reduced cardiovascular death (HR, 95% CI: 0.73 [0.54–0.98], and 0.58 [0.42–0.80]) and reduced all-cause mortality (HR, 95% CI: 0.70 [0.59–0.83], and 0.61 [0.51–0.73]). Change in BMI, however, was not a predictor of mortality once adjusted for possible confounders and fitness change.

**Conclusions:** This study had several thought-provoking findings. First, it showed that cardiorespiratory fitness and its dynamic changes are important predictors of cardiovascular and all-cause mortality. Second, once adjusted for cardiorespiratory fitness, BMI had no predictive role for mortality. These findings suggest that strategies that help maintain or improve cardiorespiratory fitness may lower the risk of cardiac and all-cause death. However, prior to widespread implementation, such assumptions need to be confirmed in well-designed comparative effectiveness trials. Further, since this study focused on men, findings cannot be extrapolated to women.48

**Effects of Weight Loss and Long-Term Weight Maintenance With Diets Varying in Protein and Glycemic Index on Cardiovascular Risk Factors: the Diet, Obesity, and Genes (DiOGenes) Study: a Randomized, Controlled Trial**

**Summary:** Although the role of different types of fat on cardiovascular risk factors has been addressed previously,49 limited studies have evaluated the roles of carbohydrate quality and of protein intake. The authors of this subanalysis from the Diet, Obesity, and Genes study (DiOGenes) study sought to separately examine the effects of either weight loss or diets varying in protein content and glycemic index without further changes in body weight on cardiovascular risk factors. DiOGenes is a pan-European controlled dietary intervention study in 932 overweight adults who first lost body weight on an 8-week low-calorie diet and were then randomized to 1 of 5 ad libitum diets for 26 weeks. The diets were either high or low protein or high or low glycemic index in 4 combinations or control. After the initial low-calorie diet phase when weight loss was substantial (-11.23 kg; P<0.001), weight regain was 0.93 kg less in high-protein versus low-protein diet groups (P=0.003) and 0.95 kg less in low-glycemic-index versus high-glycemic index groups (P=0.003) during the maintenance phase. Furthermore, in the initial period, weight loss was noted to decrease high-sensitivity C-reactive protein, low- and high-density lipoprotein cholesterol, triglycerides, and blood pressure. During the 26-week weight maintenance period in the intention-to-treat analysis, the further decrease of high-sensitivity C-reactive protein blood levels was -0.46 mg/L greater in the groups assigned to low-glycemic-index diets than in those on high-glycemic-index diets (P<0.001). Groups on low-protein diets achieved a -0.25 mg/L greater reduction in high-sensitivity C-reactive protein than those on high-protein diets (P<0.001), whereas lipid profiles and blood pressure were not differently affected.

**Conclusions:** This large-scale randomized controlled trial from Europe investigated the effect of diet composition modification, separate from caloric restriction and weight loss, on cardiovascular risk factors in obese/overweight adults. Although decrease in body weight is known to inhibit inflammatory pathways,50 the findings of this study demonstrate a further reduction of CRP levels with a low glycemic-index diet during long-term maintenance of weight loss, highlighting the significance of modest dietary changes on cardiovascular risk factors.51 A paradoxical favorable effect of CRP reduction with a low protein diet was also observed which may need to be validated in further studies. In general, findings from this study reinforce the 2010 Dietary Guidelines for Americans that lay out practical strategies for incorporating low glycemic index foods in the diet.47 However, it should be noted that this study evaluated surrogate outcomes and may not necessarily translate into improved cardiovascular health, particularly in the light of findings from the recent LookAHEAD trial, in which weight loss in diabetics did not lead to improved cardiovascular outcomes.52,53

**Lifestyle Factors in Relation to Heart Failure Among Finnish Men and Women**

**Summary:** Evidence regarding the specific role of lifestyle factors in preventing heart failure is limited. This population-based study from Finland included 18,346 men and 19,729 women who were 25 to 74 years of age and free of HF at baseline. Cross-sectional population-based health examination surveys were utilized to collect information about lifestyle factors and were then linked to national registry databases to determine HF outcomes and mortality. The authors used multivariable Cox proportional hazards regression models to examine the association between lifestyle factors (smoking, BMI, physical activity, vegetable consumption, fruit consumption, and alcohol consumption) and HF risk. During a median follow-up of 14.1 years (IQR, 5.9 to 20.9 years), 638 men and 445 women developed HF. As compared with a BMI<25, the HRs for BMI>30 were 1.75 and 2.06 in men and women respectively. Similarly, smoking, physical activity and vegetable consumption were all significant predictors of HF incidence. No significant associations were found between fruit and alcohol consumption and the risk of HF and these were dropped from the model. For the 4 modifiable lifestyle factors (smoking, BMI, physical activity, and vegetable intake), the multivariable-adjusted HRs of HF associated with engaging in 0, 1, 2, 3, and 4 healthy lifestyle behaviors compared with never smoking and BMI<25 were 1.00, 0.69, 0.45, 0.34, and 0.31 (P<0.001 for trend) for men, and 1.00, 0.53, 0.42, 0.24, and 0.19 (P<0.001 for trend) for women, respectively.

**Conclusions:** The authors of this prospective observational study from Finland demonstrated a qualitative and quantitative role of a healthy lifestyle (no smoking, low BMI, increased physical activity and increased vegetable intake) in reducing risk of incident HF uniformly for men and women. These findings corroborate with a recent study from the US that revealed a markedly decreased risk of HF hospitalization among the elderly associated with greater physical fitness levels.53 Interestingly, obesity almost doubles the risk of incident HF suggesting a promising role of optimal weight maintenance in decreasing public health burden of HF in the US where 2 in 3 individuals are either overweight or obese. Although the favorable
Body Mass Index, Surgery, and Risk of Venous Thromboembolism in Middle-Aged Women: A Cohort Study

Summary: Obesity and surgery are well-established risk factors of venous thromboembolism (VTE), though few studies have examined how obesity is independently associated with VTE with and without surgery, and whether obesity also indirectly contributes to VTE risk by increasing the risk for surgery. The authors prospectively examined a cohort of 1.3 million women recruited between 1996 and 2001 (Million Women Study through National Health Service Breast Screening program in England and Scotland) and who were followed for an average of six years. After excluding individuals with previous episodes of VTE or other major risk factors for VTE such as cancer (remaining overall cohort n=1,170,495), 4.585 women without surgery had a hospital admission with or died of VTE (0.39%); 640,288 (55%) had at least one hospital admission for surgery during follow-up of which 1,853 (0.29%) experienced an VTE during the first 12 postoperative weeks. After adjusting for major risk factors of VTE such as baseline physical activity, age, and smoking, three relationships were found: First, the risk of VTE without preceding surgery increased with BMI category, such that women with BMI of at least 35 were 3-4 times as likely as women with a body mass index of 22.5 through 24.9 to develop VTE (RR 3.35; 95% CI 3.09–3.66). Second, the risk of being admitted to hospital for surgery also increased with increases in BMI. Women who were overweight and obese were more likely to be admitted to hospital for day (RR 1.10; 95%CI 1.09–1.11) or inpatient surgery (RR 1.22; 95%CI 1.22–1.23), than those with BMI less than 25. Third, among those who had undergone surgery, overweight and obese women had higher risks of postoperative VTE than women of health weight, with relative risks of 1.46 (95% CI 1.31–1.63) and 1.78 (95% CI 1.57–2.01), respectively. This risk was elevated with increased BMI regardless of day and inpatient surgery.

Conclusions: Obesity contributes to risk of VTE among women by directly increasing the risk of VTE and by increasing the risk of being admitted to hospital for surgery, a well-established risk factor for VTE. This study characterizes an important association since BMI is one of the few modifiable risk factors for VTE. Despite increased use of anticoagulation therapy, VTE incidence has not changed significantly over the past 25 years, leading to speculations that increased obesity is not as common and can play a very important role in developing strategies for primary prevention of HF.

Birth Weight Predicts Risk of Cardiovascular Disease Within Dizygotic But Not Monozygotic Twin Pairs: a Large Population-Based Co-Twin-Control Study

Summary: Previous investigations suggest an inverse association between birth weight and risk of incident cardiovascular events. The authors used the data from the Swedish Twin Registry and determined the association between differences in birth weight with cardiovascular disease (n=3884), coronary heart disease (n=2668), and stroke (n=1372) among non-identical same sex twins, as well as identical twins. For each outcome, twins were followed for over 30 years until one of them developed the outcome. Inverse associations were observed between birth weight and risk of cardiovascular disease (odds ratio [95% CI] per each 1-kg increase in birth weight: 0.73 [0.57–0.92] for cardiovascular disease, 0.74 [0.56 to 0.98] for coronary heart disease and 0.57 [0.37 to 0.88] for stroke) for non-identical twins. However, such associations were not confirmed among identical twins (odds ratio [95% CI] per each 1-kg increase in birth weight: 0.93 [0.65–1.32] for cardiovascular disease, 1.10 [0.73 to 1.68] for coronary heart disease, and 0.92 [0.48–1.80] for stroke).

Conclusions: This study suggested an inverse link between birth weight and cardiovascular disease among non-identical twins but not among identical twins. The findings may suggest that common underlying fetal, including genetic, or maternal and placental factors that also influences birth weight may play a role in subsequent development of cardiovascular events. However, differences in postnatal care and exposures among non-identical twins are other possible explanations for this association.

Metabolic Syndrome in Adolescence: Can it be Predicted From Natal and Parental Profile? The Prediction of Metabolic Syndrome in Adolescence (PREMA) Study

Summary: The metabolic syndrome (MetS) in childhood and adolescence, which is associated with adult MetS, atherosclerosis, and type 2 diabetes mellitus, has grown in prevalence to about 10% in the United States and Western Europe, but little is known about risk factors for MetS before adulthood. This study sought to construct and test the accuracy of a risk score for MetS in Greek adolescents in 2 phases. The phase 1 derivation cohort (n=1270 children) was a prospective study which associated baseline natal, parental, and childhood characteristics of children 6–8 years old in 2000 with a 7-year follow-up into adolescence for the development of MetS. Phase 2 was a validation cohort to test the predictive accuracy of this risk score in an independent adolescent population (n=1091) from 2008–2010. Of the phase 1 cohort, 105 (8%) developed MetS in adolescence. Birth weight percentile showed an inverse relationship between BMI and odds ratio for MetS, from an odds ratio of 15 (95%CI 5.3, 39.7) in the <10th percentile of BMI down to 2.1 (0.6, 7.2) in the 75th–90th percentile. Independent predictors of MetS by multiple logistic regression analysis included birth weight <10th percentile, birth head circumference <10th percentile, and parental overweight or obesity in at least 1 parent. Using all 3 factors to predict the development of MetS in the validation cohort of adolescents showed a sensitivity of 91% (83%–95%), specificity of 98% (97%–98%), positive predictive value of 77% (67%–84%), and negative predictive value of 99% (98%–99%).

Conclusions: In the growing epidemiologic challenge presented by the metabolic syndrome in developed nations, these study results suggest that natal and parental factors, particularly weight—low birth weight in children and high body weight in parents—may help identify those at highest risk of developing adolescent MetS. The risk score proposed by these authors may provide an early framework and foundation for considering risk factor modification beginning early in life. However, given the limited sample size and the fairly homogenous cohorts of Greek Caucasian adolescents, further longitudinal studies for validation may be needed before clinical utilization of such a risk score in the general population.

Associations of Maternal Prepregnancy Body Mass Index and Gestational Weight Gain With Adult Offspring Cardiometabolic Risk Factors: the Jerusalem Perinatal Family Follow-Up Study

Summary: Maternal obesity and excess pregnancy weight gain is associated with increased weight in offspring at birth and childhood, though it remains unclear whether this association persists into...
adulthood and whether this leads to adverse cardiovascular-risk factors in adult life. This prospective study assesses the long-term association between maternal pre-pregnancy body mass index (mpBMI) and gestational weight gain (GWG) and cardiometabolic outcomes in offspring in early adulthood. The authors used a birth cohort of 1400 adults born in Jerusalem who had extensive archival data and clinical information at 32 years of age as part of the Jerusalem Perinatal Family Follow-Up Study. Higher mpBMI, independent of GWG and confounders, was significantly associated with higher offspring BMI, waist circumference, and multiple cardiometabolic risk factors. Compared to offspring of mothers with mpBMI with the lowest quintile (<21.0 kg/m²), those with mothers in the highest quintile (>26.4 kg/m²) had 5 kg/m² higher mean BMI, 8.4 cm higher waist circumference, 11.4 mg/dL higher triglycerides, and 3.8 mg/dL lower HDL. Likewise GWG, independently of mpBMI, was associated with increased offspring BMI and waist circumference—differences of 1.6 kg/m² in BMI and 2.4 cm in waist circumference were observed when comparing offspring of mothers in the highest and lowest quintiles (GWG>14 kg and <9kg, respectively).

Conclusions: Excess maternal body mass and weight gain during pregnancy are associated with increased weight and other adverse cardiometabolic measures in adult offspring. However, the mechanism remains unclear. The change may be due to an epigenetic mechanism triggered during pregnancy leading to increased lifetime risk of obesity. The deleterious effects of high body weights on cardiovascular health are well known with increasing BMI being associated with cardiovascular disease, type 2 diabetes mellitus, obstructive sleep apnea, hypertension, heart failure as well as all-cause mortality. While significant progress has been made understanding the pathophysiological mechanisms leading to body weight phenotypes and obesity in particular, significant knowledge gaps persist. The interactions between a myriad of genetic, environmental, behavioral or cultural factors and their net effect on final phenotype need to be clearly elucidated. Additionally, there is a constant search for possible new factors predisposing to obesity in children and adults alike. For example, there is emerging evidence of the effect of exposure to maternal hyperglycemia during pregnancy leading to increased lifetime risk of obesity. On the genetics front, multiple new genetic loci have been identified in recent times. However, it is unknown to what extent these genetic factors play a role in determining the BMI of an individual.

Keeping this background in mind, in the following section we review research that examines the interaction between genetic factors and lifestyle decisions, as well as effect of exposure to maternal diabetes on offspring BMI.

Television Watching, Leisure Time Physical Activity, and Genetic Predisposition in Relation to Body Mass Index in Women and Men

Summary: In studies on gene-lifestyle interaction and obesity, there has been little attention paid to the effect of sedentary behavior as indicated by television (TV) watching. The authors therefore studied the interactions between genetic predisposition, TV watching, and leisure time physical activity and BMI in 7740 women and 4564 men from two prospective cohort studies – the Health Professionals Follow-up Study and The Nurses’ Health Study. Data on TV watching and physical activity were collected two years before BMI assessment, and, using BMI-associated genetic variants, a weighted genetic score was calculated. In both men and women, the genetic association with BMI strengthened with more hours of TV watching, as an increment of 10 points in the genetic risk score across five categories of TV watching (0–1, 2–5, 6–20, 21–40, and >40 hours/week) was associated with 0.8 (SE, 0.4), 0.8 (SE, 0.2), 1.4 (SE, 0.2), 1.5 (SE, 0.2), and 3.4 (SE, 1.0) kg/m² higher BMI (P for interaction = 0.001). On the other hand, the genetic association with BMI weakened with increased levels of physical activity, with an increment of 10 points in genetic risk across quintiles of physical activity associated with 1.5 (SE, 0.2), 1.3 (SE, 0.2), 1.2 (SE, 0.2), 1.2 (SE, 0.2), and 0.8 (SE, 0.2) kg/m² higher BMI scores (P for interaction < 0.001). In addition, the interactions of physical activity and TV watching with genetic predisposition with respect to BMI were independent of one another.

Conclusions: This study suggests that prolonged television watching, indicating a sedentary lifestyle, may heighten the genetic predisposition to adiposity, while more leisure time physical activity may lessen the impact of the genetic association with obesity. Therefore, the final outcome of adiposity is highly likely to be modified by environmental factors and lifestyle choices in both positive and negative ways. It is notable that the participants in the study were genetically inferred to have European ancestry, so it remains to be seen whether these results can be generalized to other ethnic groups. However, from a public health standpoint, this study offers increasing exercise levels and reducing sedentary behaviors as possible methods of environmental change that can mitigate the genetic predisposition to increased BMI.

Association of Maternal Diabetes Mellitus in Pregnancy With Offspring Adiposity into Early Adulthood Sibling Study in a Prospective Cohort of 280 866 Men From 248 293 Families

Summary: Maternal diabetes mellitus (DM) in pregnancy is known to result in greater offspring adiposity at birth. However, the long-term effects on offspring adiposity are unknown. The authors investigated whether maternal DM had a significant effect on long-term adiposity of their offspring, and, if such an effect was present, whether it was mediated through intra-uterine mechanisms, environmental risk factors or combination of both. The study database was constructed by linking records from a prospective study cohort of 280,866 singleton-born Swedish men from 248,293 families who completed their conscription medical examination to multiple national Swedish registries. They built separate analytical models to investigate the effect of maternal DM. The initial model examined effect of maternal DM within siblings effectively controlling for common fixed maternal characteristics (socioeconomic background, lifestyle and maternal genes) to isolate possible independent in-utero effect. A separate regression model was built examining maternal DM among non-related individuals. Variables added to both the models included year of birth, maternal age at birth, parity, and maternal educational status, as well as offspring’s birth weight and gestational age. Maternal DM during pregnancy was noted to be associated with greater mean BMI at age 18 in their sons. This effect was consistent across the study cohort including siblings as well as non-siblings, with maternal DM leading to an average increase of 1.00 kg/m² (95% CI, 0.81 to 1.18) at age 18 in their offspring. Interestingly, BMI of men whose mothers had diabetes mellitus during their pregnancy was on average 0.94 kg/m² greater (95% CI, 0.35 to 1.52) than in their brothers born before their mother was diagnosed with diabetes. These effects persisted in spite of additional adjustment for maternal BMI during pregnancy. Finally, maternal BMI was positively associated with son’s BMI between unrelated individuals, but there was no association within brothers.

Conclusions: Utilizing Sweden’s multiple national registries, the authors suggest that diabetes during pregnancy increases the lifetime risk of developing obesity in their offspring. This could be mediated by factors such as the maternal genotype inherited by the offspring or
dietary/lifestyle habits the offspring is exposed to during adolescence. Additionally, the discordant BMI rates in brothers based on maternal DM exposure, demonstrate that certain poorly understood in-utero mechanisms might play a role as well. Overall, a challenging study to conduct, it raises the intriguing possibility that early diagnosis and treatment of maternal DM may prevent possible long-term detrimental health effects on their offspring.69

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