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# Clinical functional and genetic predictors of ischemic heart disease in the context of obesity (Literature review)

**O.G. Tilepbaeva, S.K.Nuritdinova**
**Tashkent Medical Academy**

## Annotation

Obesity has emerged as a significant risk factor for ischemic heart disease (IHD), particularly in western countries where the availability of energy-dense processed foods has led to increased prevalence rates. This rise in obesity prevalence in diverse populations highlights the importance of understanding clinical, functional, and genetic predictors of IHD in the context of excess adiposity. While traditional health risks associated with obesity, such as type 2 diabetes and hypertension, are well-recognized, emerging research indicates that factors like fat distribution, metabolic profiles, and genetic predispositions play crucial roles in determining individual risk for IHD.

The relationship between obesity and cardiovascular health is complex; studies show that visceral fat, as indicated by waist circumference, is a better predictor of cardiovascular risk than body mass index (BMI) alone. Additionally, recent findings suggest that insulin resistance is critically linked to both obesity and the development of IHD, with variations in individual responses to weight and fat distribution further complicating risk assessment.

Research exploring the genetic underpinnings of obesity-related IHD is expanding, revealing various susceptibility loci that may influence disease progression in different populations. Notably, the interaction between lifestyle factors—such as physical activity—and genetic predispositions can shape the trajectory of IHD risk among individuals with obesity.

Furthermore, recent studies underscore the importance of holistic approaches combining clinical assessments, metabolic profiling, and genetic screening for accurately identifying individuals at high risk for IHD. Despite advancements in treatment options, including statin therapy, the efficacy of these interventions in obese populations presents ongoing challenges, necessitating further research to optimize management strategies and improve patient outcomes. Understanding these complex interrelations can lead to better prevention and therapeutic measures for ischemic heart disease that consider individual patient profiles within the context of obesity.

**Keywords:** obesity, coronary heart disease, insulin resistance, waist circumference, body mass index, adiposity, physical inactivity, cardiovascular disease, genetic predisposition, nutrition, processed foods, visceral fat, metabolic health, ethnopharmacology, lifestyle interventions, health risks, preventive strategies, statin therapy, health expenditure, epidemiology.

Obesity has always existed in human populations, but until very recently it was comparatively rare. The availability of abundant, energy-rich processed foods in the last few decades has resulted in a sharp rise in the prevalence of obesity in westernized countries. Although it is the obesogenic environment that has contributed to this major healthcare problem, it is acting by revealing a sub-population with a pre-existing genetic predisposition to excess adiposity. There is substantial evidence for the heritability of obesity, and research into both rare and common forms of obesity has

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identified genes with significant roles in its etiology. The application of this understanding to patient care has been slower. Until very recently, the health risks of obesity were thought to be well understood, with a straightforward correlation between increasing obesity and increasing risk of health problems such as type 2 diabetes, coronary heart disease, hypertension, arthritis, and cancer. It is becoming clear, however, that the location of fat deposition, variation in the secretion of adipokines, and other factors govern whether a particular obese person develops such complications. Prediction of the health risks of obesity for individual patients is not straightforward, but continuing advances in our understanding of genetic factors influencing obesity risk and improved diagnostic technologies suggest that the future for such prediction is looking increasingly bright.

According to the World Health Organization, the escalating international epidemic of obesity is now the most significant contributor to ill health. More than 30% of US adults are obese, defined as a body mass index (BMI) of ≥30 kg/m², and it is feared that one in three children born in the early 21st century will develop diabetes with a consequent reduction in lifetime expectancy. Obesity accounts for 5–7% of national health expenditure in the US and now outranks both smoking and drinking in its deleterious effects on health and health costs. Prevalence levels in the UK are following closely behind. The pediatric picture is just as gloomy with a 2–2.8-fold increase over a 10-year period in childhood obesity [1].

There is a strong correlation between overall obesity and abdominal obesity; however, some individuals may be classified as having overall obesity but not abdominal obesity. Conversely, there may also be individuals with abdominal obesity in the absence of overall obesity based on the BMI definition of obesity. The presence of cardiometabolic disease and cardiovascular disease (CVD) in those with "normal weight obesity" leads to misclassification and underdiagnosis of CVD risk in clinical practice, particularly among patients who have excess fat but are not classified as obese by BMI. Thus, high waist circumference (WC), even in individuals with normal weight, may unmask higher CVD risk because WC is an indicator of abdominal body fat, which is associated with cardiometabolic disease and CVD and is predictive of mortality. WC, as a measure of abdominal obesity, provides an indicator of body composition and adds critical information along with BMI. Several organizations and expert panels have recommended that WC measures be assessed along with BMI in clinical evaluations because increasing evidence supports visceral adiposity as a marker of cardiovascular risk. The development of imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) has been a remarkable advance in the study of human body composition and its relationship with CVD risk. With these methods, cross-sectional images of the body at any level allow the quantification of areas or volumes of various adipose tissue and ectopic fat depots. An ectopic fat depot is generally considered a lipid deposit that is not physiologically stored in adipose tissues, such as in the liver, pancreas, heart, and skeletal muscle. Cohort imaging studies have shown that all adipose and ectopic fat depots are correlated with one another. However, at any BMI or total adiposity level, there is considerable individual variation in the amount of subcutaneous versus intra-abdominal or visceral adipose tissue (VAT) in the abdominal cavity. There may be a 2- to 3-fold variation in the amount of VAT at any level of total or subcutaneous adiposity. Within overweight and obese categories, individuals with low levels of VAT are characterized by a more favorable CVD risk profile, sometimes referred to as metabolically healthy obesity. Recent data suggest that metabolically healthy obesity may be a transient phenotype for the majority of the population, with the duration of metabolically healthy obesity differing by race/ethnicity and sex [2].

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The results of the current population-based study provide additional insight into the relationship between obesity and insulin resistance and are reasonably similar to the only published study in which this relationship has been evaluated in a large number of individuals using a specific method to determine insulin-mediated glucose disposal. In addition to supporting previous results that differences in weight modulate insulin action, the data presented provide a quantitative estimate of the role of obesity in regulating insulin-mediated glucose disposal. The relationship between BMI and SSPG shown in Figure 1 and Table 1 indicates that only approximately 22% of the variability in SSPG concentration ($r^2$) in this healthy volunteer population can be attributed to differences in BMI, an estimate that is consistent with the report of the European Group for the Study of Insulin Resistance (EGIR). This group quantified insulin action in 1,146 nondiabetic, normotensive individuals with the euglycemic, hyperinsulinemic clamp and defined insulin resistance as the value of insulin-mediated glucose disposal in the lowest 10% of the normal weight population (BMI < 25.0 kg/m²). With this criterion, they found that 26% of the obese individuals (BMI ≥ 29.0 kg/m²) to be insulin-resistant [3].

Obesity, traditionally defined as an excess of body fat causing prejudice to health, is usually assessed in clinical practice by the body mass index (BMI), which is expressed as the ratio of body weight in kilograms divided by height in square meters (kg/m²). Since its introduction, many large population studies have reported a J-shaped relationship between BMI and mortality/morbidity risk—a BMI above 30 kg/m² (defining obesity in many guidelines) being clearly associated with increased morbidity/mortality risk. Despite its limitations, BMI has been adopted as a quick and simple clinical tool to first classify patients into risk categories and to monitor changes in adiposity over time at both the individual and population levels. Despite considerable research efforts devoted to understanding the biology of obesity and energy balance, it has become obvious that available knowledge has to date been of little help in curbing the obesity epidemic and that no part of the world has been spared from this phenomenon. It has been estimated by the Global Burden of Disease Obesity Collaborators that over 603.7 million adult individuals are obese. The Global Burden of Disease group has also estimated that elevated BMI values were responsible for 4 million deaths in 2015, with two-thirds of this number attributed to cardiovascular disease (CVD). In the United States, the prevalence of obesity reached almost 40% in 2015 to 2016 in a nationally representative survey (National Health and Nutrition Examination Survey). Furthermore, severe obesity (class III and above), defined by a BMI ≥40 kg/m², has been reported to reach 7.7% with considerable disparities among ethnic groups [4].

Both obesity and physical inactivity are recognized as major risk factors for the development of coronary heart disease (CHD), and modifying these factors is considered an effective lifestyle intervention for CHD prevention. However, the relative importance of obesity and physical activity as predictors of CHD risk remains controversial. In a recent report, Wessel et al. found that among 906 women undergoing coronary angiography or suspected ischemia, self-reported physical fitness scores but not measures of obesity were independently associated with CHD incidence. This study was relatively small, however, and most women had existing coronary disease at baseline. Thus, it is not clear whether the results apply to healthy women. Recently, we reported that body mass index (BMI) and physical activity independently predicted total and cause-specific mortality. In the present study, we examined independent and joint associations of physical activity and adiposity measures (BMI, waist circumference, and waist-to-hip ratio [WHR]) with incidence of CHD during 20 years of follow-up in the Nurses' Health Study (NHS).

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Physical activity measures were described in detail previously. Women were first asked about physical activity on the 1980 questionnaire. They were asked to report the average number of hours spent each week during the past year on moderate (e.g., brisk walking) and vigorous recreational activities (e.g., vigorous sports and jogging). A similar question was included in the 1982 questionnaire. In 1986, 1988, 1992, 1996, and 1998, women were asked to report the average time spent per week on the following activities: walking, jogging, running, bicycling, lap swimming, playing tennis or squash, and participating in calisthenics. Using this information, we calculated the average amount of time per week spent on moderate-to-vigorous activities (requiring 3 or more metabolic equivalents per hour, including brisk walking) at each time point. Our validation study indicated relatively good validity and reproducibility for the questionnaire. The correlation between physical activity reported on 1-week recalls and that reported on the questionnaire was 0.79. The correlation between moderate to vigorous activity reported in diaries and that reported on the questionnaire was 0.62. In a separate population aged 20 to 59 years, recruited from a university community (n=103), the correlation between the physical activity score on a very similar questionnaire and maximum oxygen consumption was 0.54 [5].

Coronary heart disease continues to be a leading cause of morbidity and mortality among adults in Europe and North America. Risk factors have included blood pressure, cigarette smoking, cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and diabetes. Factors such as obesity, left ventricular hypertrophy, family history of premature CHD, and estrogen replacement therapy (ERT) have also been considered in defining CHD risk. Data from population studies have enabled the prediction of CHD during a follow-up interval of several years, based on blood pressure, smoking history, TC and HDL-C levels, diabetes, and left ventricular hypertrophy on the ECG. These prediction algorithms have been adapted to simplified score sheets that allow physicians to estimate multivariable CHD risk in middle-aged patients. The present article develops a simplified coronary prediction model, building on the blood pressure, cholesterol, and LDL-C categories proposed by the JNC-V and NCEP ATP II. The analysis evaluates the utility and accuracy of blood pressure, cholesterol, and LDL-C recommended categories in multivariable CHD prediction, using a Framingham Heart Study sample that pooled information for the original and offspring cohorts and followed them for 12 years. This approach emphasizes the established, powerful, independent, and biologically important factors. Family history for heart disease, physical activity, and obesity are not included because these factors work largely through the major risk factors, and their unique contribution to CHD prediction can be difficult to quantify. The prediction of initial CHD events in a free-living population not on medication is emphasized. Consequently, ERT for postmenopausal women, treatment of high blood pressure, and therapy for high blood cholesterol are not included in the formulations [6].

Coronary heart disease (CHD) is the leading cause of death in most industrialized countries, with a growing epidemic in low and middle-income countries. The development of the disease depends on a complex interaction between environmental and genetic factors. Modifiable risk factors such as hypertension, dyslipidemia, diabetes, obesity, and smoking can predict 80%-90% of the risk of CHD in most populations around the world. However, wide differences in CHD incidence and mortality rates between populations or ethnic groups are not fully explained by their respective distribution of traditional cardiovascular risk factors (TCRFs). Indeed, some populations may have a lower burden of CHD than others despite similar rates of TCRFs. The epidemiology of CHD in Afro-Caribbean individuals is a striking example of the disproportionate relationship between CHD

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occurrence and TCRF distribution at the population level. In the French Caribbean island of Guadeloupe, approximately 80%-85% of the population is of Afro-Caribbean origin. Although there are few smokers (15%), there is a high prevalence of hypertension (30%), diabetes (10%), and obesity (23%). However, observational data indicate lower standardized mortality rates from CHD in both men (about 50%) and women (about 40%) compared with mainland France, which has one of the lowest incidences of CHD in Europe. Similar differences between white and Afro-Caribbean communities have also been reported in the United Kingdom and remain unexplained. The study of such ethnic differences is important not only for the concerned populations but also for all populations, as it can provide key information for the management of CHD and identify new targets for treatment and preventive strategies. The lack of a strong correlation between CHD incidence and TCRFs suggests that genetic variation could lie behind the interpopulation variability in coronary mortality. In the past few years, several susceptibility loci for CHD have been identified, mostly in white populations; however, no data are available in Afro-Caribbean populations. Genetic risk scores (GRSs) could be a valuable tool to assess.

The Afro-Caribbean participants were recruited from the island of Guadeloupe, a French Caribbean region with a wide availability of health services and easy access to medical care regardless of income. All participants were Afro-Caribbeans. The ethnic origin was determined when the patient defined themselves and two first-degree relatives as Afro-Caribbean. Cases were extracted from the Department of Cardiology at the University Hospital of Pointe-à-Pitre. Patients were eligible if they had a documented history of previous acute myocardial infarction according to the World Health Organization criteria, coronary bypass surgery (or both), or coronary angioplasty. Control participants were selected from a public health center on the same island and had no suspicion or history of cardiovascular disease. TCRFs were determined using the same definition in cases and controls. Participants were considered to have hypertension if they had a history of hypertension or were prescribed antihypertensive therapy. Similarly, they were considered to have diabetes or hypercholesterolemia if they had a history of diabetes or hypercholesterolemia or were prescribed hypoglycemic agents (including insulin) or lipid-lowering therapy, respectively. Participants were considered to be current smokers if they were regularly smoking more than one cigarette per day at the time of inclusion. Body mass index (BMI) was calculated as weight/height$^2$ (kg/m$^2$), and obesity was determined by a BMI $\geq$30 kg/m$^2$. All participants gave their written informed consent to participate in the study, which received the approval of the inter-regional ethics committee (Sud-Ouest/Outre-Mer III, France). The white sample used was from the Second Northwick Park Heart Study (NPHSII) and has already been described. Briefly, 3,052 middle-aged men (50-64 years of age) with no previous history of cardiovascular disease were recruited from nine general practices in the United Kingdom. The study started in 1989, and incident cases of acute or silent myocardial infarction and coronary surgery were recorded during a median of 13.5 years of follow-up. All participants gave written informed consent, and the study was approved by the National Health Service Health Research Authority Research Ethics Committee London Central [7].

Hydroxymethylglutaryl coenzyme A reductase inhibitor (statin) therapy lowers morbidity and mortality in coronary artery disease (CAD) and other atherosclerotic vascular diseases, as evidenced by multiple large-scale clinical trials. Additional analyses of these trials have shown that statin therapy also reduces the risk of developing heart failure (HF). A reduction in cardiovascular events with statin therapy has been demonstrated irrespective of baseline low-density lipoprotein (LDL) cholesterol. Therefore, it is reasonable to hypothesize that statins would confer a survival benefit in

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patients with ischemic HF. Yet, the impact of statin therapy on HF progression has not been previously studied. The major clinical trials of statin therapy have generally excluded patients with symptomatic or severe HF. Statins have therapeutic properties that are potentially beneficial for patients with HF of ischemic and non-ischemic etiologies, irrespective of lipid levels. Statins may improve endothelial function, inhibit inflammatory cytokines, potentiate nitric oxide (NO) synthesis, restore impaired autonomic function, and reverse pathological myocardial remodeling. On the other hand, concern has also been raised about the potential adverse effects of statins in HF. Low cholesterol levels are associated with poor outcomes in advanced HF, calling into question the safety of lipid-lowering therapy in this population. Furthermore, statins decrease levels of ubiquinone (coenzyme Q10), which may impact ventricular function and exercise tolerance in HF patients. Statins are included as part of the medical regimen of only a portion of patients with CAD and HF. One-third of ischemic HF patients in one large population cohort and between 11% to 45% of patients in large HF clinical trials were treated with statins. Based on autopsy data, up to 33% of the deaths in HF patients are related to acute coronary syndromes. If statin therapy is safe and effective in reducing acute coronary events in patients with HF, millions of HF patients who would benefit from such therapy are not currently being treated. Alternatively, if statins have adverse effects in HF, a large number of HF patients are being exposed unnecessarily. In light of the controversy surrounding statin use in patients with HF, and without the results of ongoing clinical trials, we undertook the present study to evaluate the effect of statin therapy in a large, diverse cohort of patients treated for advanced HF of multiple etiologies at a single university center [8]

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