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The role of insulin resistance in the association between body fat and autonomic function

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Abstract *Background and aim:* Excess body fat is associated with altered autonomic function. We investigated whether this association is mediated by insulin resistance.
Methods and results: Cross-sectional analysis of a subgroup of the Netherlands Epidemiology of Obesity study with measurements of autonomic function (heart rate variability calculated as mean interbeat interval, standard deviation of all normal intervals (SDNN), low frequency (LF) power and high frequency (HF) power). We measured BMI(kg/m^2), total body fat(%) and waist circumference(cm), and calculated the HOMA-index of insulin resistance (HOMA-IR). We examined the association between body fat and heart rate variability with multivariate linear regression analysis. To investigate whether the association was mediated by insulin resistance, we additionally adjusted for HOMA-IR.

After exclusion of participants with glucose lowering medication (n = 19), 466 participants were included. Per SD of BMI, the difference in SDNN was −2.7% (95%CI: −5.5, 0.1) in the multivariate model. Additional adjustment for HOMA-IR attenuated this association to −1.2% (95%CI: −4.2, 1.7), suggesting that 55% of the association between BMI and SDNN was mediated by HOMA-IR. All measures of body fat were associated with mean interbeat interval, SDNN and LF power. Depending on the parameter of body fat or heart rate variability, 29–81% of the association was mediated by HOMA-IR.
Conclusion: In this cross-sectional study, body fat was associated with heart rate variability. This association may at least partially be mediated by insulin resistance. Future studies should investigate whether a reduction in obesity and insulin resistance may prevent the adverse cardiovascular consequences of altered autonomic function.

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Introduction

Excess body fat is associated with altered function of the autonomic nervous system and sympathetic activation [1,2]. Altered autonomic function is an independent risk factor for cardiovascular events in populations with prevalent cardiovascular disease [3,4], but also for a first event in the general population [5]. The mechanism underlying the association between body fat and altered autonomic function is not elucidated. We hypothesize that insulin resistance may be the underlying factor (Fig. 1).

Obesity, especially abdominal obesity, is a risk factor for insulin resistance [6,7]. Insulin resistance has also been associated with altered autonomic function in several cross-sectional studies [8–12]. Based on the results of these cross-sectional results, it remained unclear whether insulin resistance alters autonomic function, or vice versa. We however recently showed that autonomic function was not prospectively associated with the incidence of type 2 diabetes mellitus during a median follow up of 9.2 years [13]. This suggests that the autonomic nervous system may not be involved in the development of insulin resistance, and supports a pathophysiological mechanism in which insulin resistance is the first abnormality in obesity, resulting in sympathetic activation. This mechanism is further supported by the physiological reactions of the autonomic nervous system to infusions of blood glucose and insulin in humans [14,15].

Therefore, our aim was to study the role of insulin resistance as a mechanism underlying the association between body fat and autonomic function (Fig. 1). To that extent, we investigated the association between measures of body fat and parameters of autonomic function and whether this association was mediated by insulin resistance.

Methods

Study design and population

The Netherlands Epidemiology of Obesity (NEO) study is a population-based prospective cohort study comprising 6673 persons with an oversampling of individuals with a BMI $\geq$ 27 kg/m^2. The study design and data collection of the NEO study have been described previously [16]. In short, persons aged between 45 and 65 years with a self-reported BMI of 27 kg/m^2 or higher were included between September 2008 and October 2012. In addition, all inhabitants aged between 45 and 65 years from one municipality (Leiderdorp) were invited irrespective of their BMI, allowing for a reference distribution of BMI.

The baseline visit was performed in the NEO study centre in the Leiden University Medical Centre, during which an extensive physical examination was performed. The present study is a cross-sectional analysis of baseline measurements of the participants with a measurement of heart rate variability. We additionally excluded participants who were using oral glucose lowering medication or insulin. The NEO study was approved by the Medical Ethical Committee of the Leiden University Medical Centre and all participants gave their informed consent.

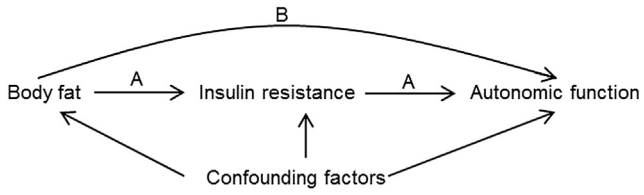

Figure 1 Hypothesized path diagram. Confounding factors: age, sex, tobacco smoking, ethnicity, education, physical activity, prevalent cardiovascular disease and cardiac medication. A, indirect association between body fat and autonomic function (mediated by insulin resistance) B, direct association between body fat and autonomic function A + B, total association between body fat and autonomic function.

Data collection

Participants reported their highest level of education in ten categories according to the Dutch educational system. We grouped these data into low education (defined as no education, primary education or lower vocational training) versus high education (used as the reference category). Tobacco smoking was categorized into current, former or never (reference) smokers. Self-reported pre-existing cardiovascular disease was defined as myocardial infarction, angina, congestive heart failure, stroke, or peripheral vascular disease. Participants reported the frequency and duration of their physical activity using the Short Questionnaire to Assess Health-enhancing physical activity (SQUASH) questionnaire. We calculated the total energy expended during physical activity in hours per week of metabolic equivalents (MET-h/week).

Body fat

We measured height and weight without shoes and 1 kg was subtracted to correct for the weight of clothing. Body Mass Index (BMI) was calculated by dividing the weight in kilograms by the height in meters squared. Total body fat was measured using a bio-impedance device (TBF-310, Tanita International Division, United Kingdom). We measured the circumference of the waist with a flexible tape in the middle of the distance between the lowest rib and the crista iliaca and used this as a measure of abdominal fat mass.

Insulin resistance

Venous blood was sampled after an overnight fast for at least 10 h. Plasma glucose concentrations were measured with the enzymatic and colorimetric method (Roche Modular Analytics P800, Roch Diagnostics, Mannheim, Germany) and serum insulin concentrations were determined by an immunometric method (Siemens Immulite 2500, Siemens Healthcare Diagnostics, Breda, the Netherlands). We calculated the updated Homeostasis Model Assessment Insulin Resistance (HOMA-IR), a