Clinical Science

Characterization of metabolically unhealthy normal-weight individuals: Risk factors and their associations with type 2 diabetes

CrossMark

Nathalie Eckel[a,b], Kristin Mühlenbruch[a,b], Karina Meidtner[a], Heiner Boeing[c], Norbert Stefan[b,d,e], Matthias B. Schulze[a,b,*]

[a] Department of Molecular Epidemiology, German Institute of Human Nutrition Potsdam-Rehbrücke, Nuthetal, Germany
[b] German Center for Diabetes Research (DZD), Germany
[c] Department of Epidemiology, German Institute of Human Nutrition Potsdam-Rehbrücke, Nuthetal, Germany
[d] Institute of Diabetes Research and Metabolic Diseases (IDM) of the Helmholtz Center München at the University of Tübingen, Tübingen, Germany
[e] Department of Internal Medicine IV, University Hospital of Tübingen, Tübingen, Germany

ARTICLE INFO

ABSTRACT

Objective. A proportion of type 2 diabetes cases arise from normal-weight individuals who can therefore be considered to be "metabolically unhealthy normal-weight" (MUH-NW). It remains unclear which factors account for this access risk. Our aims were to identify risk factors for type 2 diabetes in normal-weight individuals and to compare the strengths of their associations with type 2 diabetes to that observed in overweight and obese participants.

Methods. A case-cohort, including 2027 sub-cohort participants and 706 incident type 2 cases, was designed within the population-based European Prospective Investigation into Cancer and Nutrition Potsdam study. Adjusted means and relative frequencies of anthropometric, lifestyle and biochemical risk factors were calculated in groups stratified by BMI and incident diabetes status. Cox regressions were applied to evaluate associations between these variables and diabetes risk stratified by BMI category.

Results. MUH-NW individuals were characterized by known diabetes risk factors, e.g. they were significantly more likely to be male, former smokers, hypertensive, and less physically active compared to normal-weight individuals without incident diabetes. Higher waist circumference (women: 75.5 vs. 73.1 cm; men: 88.0 vs. 85.1 cm), higher HbA$_{1c}$ (6.1 vs. 5.3%), higher triglycerides (1.47 vs. 1.11 mmol/l), and higher levels of high sensitive C-reactive protein (0.81 vs. 0.51 mg/l) as well as lower levels of HDL-cholesterol (1.28 vs. 1.49 mmol/l) and adiponectin (6.32 vs. 8.25 μg/ml) characterized this phenotype. Stronger associations with diabetes among normal-weight participants compared to overweight and obese (p for interaction < 0.05) were observed for height, waist circumference, former smoking, and hypertension.

Conclusions. Normal-weight individuals who develop diabetes have higher levels of diabetes risk factors, however, frequently still among the normal range. Still, hypertension, elevated HbA$_{1c}$ and lifestyle risk factors might be useful indicators of risk.

1.　Introduction

Obesity is an established risk factor for type 2 diabetes. Consequently, BMI as the most frequently used diagnostic tool for the measurement of obesity is also typically associated with type 2 diabetes [1]. However, 15–20% of incident diabetes cases arise from normal-weight individuals in prospective studies [2,3]. Normal-weight individuals (BMI <25 kg/m^2) who are at increased risk for metabolic disorders like type 2 diabetes can be considered to be "metabolically unhealthy normal-weight" (MUH-NW) or "metabolically obese normal-weight". This phenotype was first mentioned in the 1980's by Rudermann et al., who also proposed them to be characterized by hyperinsulinemia, insulin resistance, and hypertriglyceridemia [4], parameters that might also separate metabolically unhealthy from metabolically healthy obesity [5,6]. In fact, recent cohort studies indicated a greater diabetes risk for MUH-NW, defined by the presence of metabolic syndrome or insulin resistance, compared to metabolically healthy normal-weight individuals [7–12]. However, the majority of incident diabetes cases among normal-weight participants in these studies were neither insulin resistant nor had the metabolic syndrome, suggesting that other factors might be important to identify normal-weight individuals at an increased risk. For example, further research indicated that also physical inactivity, abdominal fat accumulation, smoking and oxidative stress parameters are correlated with MUH-NW, defined a priori by certain criteria [13–15]. However, there is still uncertainty regarding criteria for the definition of a "metabolically unhealthy normal-weight" state, even though a thoughtful definition is essential to find people at risk [16].

Several risk factors beyond overweight are linked to type 2 diabetes, e.g. body fat distribution, lifestyle-related and dietary variables [17]. Nevertheless, it is not known so far which of these factors are contributing to an elevated diabetes risk in normal-weight individuals. Also, the associations of risk factors and diabetes risk may differ between normal-weight and overweight or obese individuals. For example, the association between waist circumference and type 2 diabetes may be stronger among normal-weight individuals compared to overweight or obese individuals [18]. However, abdominal obesity is rare among normal-weight people accounting for only a fraction of incident cases observed in this group [19]. Therefore, the aim of the study was twofold: First, we aimed to characterize risk factor levels among normal-weight individuals who develop type 2 diabetes on the basis of lifestyle, anthropometric and dietary variables, as well as biomarkers. Second, we addressed the question whether associations of these known risk factors with diabetes differ in their strength or direction between normal-weight individuals and overweight or obese individuals.

2.　Material and Methods

2.1.　Study Population

The European Investigation into Cancer and Nutrition (EPIC) Potsdam Study is a prospective cohort study with baseline examinations from 1994 to 1998. 16,683 women mainly aged 35–64 years and 10,933 men mainly aged 40–64 years were recruited in Potsdam, Germany, and surrounding communities [20]. Baseline examinations included self-administered food frequency and lifestyle questionnaires as well as PC-guided interviews with questions concerning occupation, smoking history, and physical activity. Furthermore, anthropometric and blood pressure measurements were conducted and blood samples were drawn from 95.7% of the participants. For the collection of follow-up information, questionnaires were mailed to the study participants every 2–3 years with response rates exceeding 90% [21].

For the current study, a case-cohort was constructed consisting of all participants who developed incident type 2 diabetes (n = 801) during a mean follow-up of 7 years, and the sub-cohort which is a sample (n = 2500) of participants of the full cohort who provided blood samples at baseline (n =26,444), drawn with a SAS random sampling procedure. The number of participants in the sub-cohort, which correspond to 10% of the initial cohort, was based on a priori power calculation. When having a large full cohort with a low failure rate, a sampling proportion of 10% can provide similar power as well as comparable results to those of the full cohort [22,23]. Due to its random selection, the sub-cohort is representative for the full cohort at baseline [24], and therefore also includes a proportion of incident cases (so called "internal" cases, n = 74). The remaining 727 "external" cases were identified from the full cohort in individuals not selected for the sub-cohort. Participants with prevalent diabetes (N$_{sub-cohort}$ = 178) or with missing or implausible data on biomarkers (N$_{sub-cohort}$ = 295, N$_{cases}$ = 87) were excluded, leaving a case-cohort sample of 2027 participants from the sub-cohort and 706 incident cases (with an overlap of 66 internal cases between both groups). Implausible biomarker data were defined as follows: adiponectin <0.0015 μg/ml; fetuin <62.5 μg/ml; GGT = 0 U/l; triglycerides <10 mmol/l; HDL-cholesterol <0.01 mmol/l. Excluded participants did not differ in baseline characteristics from those included in the study (Supplemental Table S1). The Ethical Committee of the State of Brandenburg, Germany approved the study. All participants gave written informed consent.

2.2.　Identification of Incident Type 2 Diabetes

In follow-up questionnaires, incident diabetes was identified either by self-reported diagnosis, diabetes-relevant medication, or dietary treatment due to diabetes. Self-reports were