Parkinsonism and Related Disorders xxx (2015) 1–8

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Prospective study on the components of metabolic syndrome and the incidence of Parkinson's disease

Katri Sääksjärvi [a, *], Paul Knekt [a], Satu Männistö [b], Jukka Lyytinen [c], Markku Heliövaara [a]

[a] The Health Monitoring Unit, Department of Health, National Institute for Health and Welfare, P.O. Box 30, FI-00271 Helsinki, Finland
[b] The Chronic Disease Prevention Unit, Department of Health, National Institute for Health and Welfare, P.O. Box 30, FI-00271 Helsinki, Finland
[c] Department of Neurology, Helsinki University Central Hospital, P.O. Box 100, FI-00029 HUS, Finland

ARTICLE INFO

Article history:
Received 12 May 2015
Received in revised form
26 June 2015
Accepted 20 July 2015

Keywords:
Biological markers
Cohort studies
Metabolic syndrome
Parkinson's disease
Risk factors

ABSTRACT

Introduction: Inconsistent results regarding the association between the components of metabolic syndrome and Parkinson's disease (PD) have been reported. We investigated whether the metabolic syndrome or its components, or serum total cholesterol, predict PD incidence in a prospective cohort study design.

Methods: The study was based on the Mini-Finland Health Survey including 6641 individuals aged 30–79 and free from PD at baseline (1978–1980). During 30 years of follow-up, 89 incident PD cases occurred.

Results: After adjustment for sociodemographic and lifestyle factors, the relative risk (RR) of PD was 0.50 (95% confidence interval (CI): 0.30, 0.83) for individuals with the metabolic syndrome compared to those without. This association was especially due to elevated serum triglyceride concentration (≥1.7 vs.<1.7 mmol/L, RR = 0.52, 95%CI: 0.30–0.89, *P* for trend 0.02) and elevated plasma fasting glucose concentration (≥5.6 vs.<5.6 mmol/L, RR = 0.56 0.32, 0.98, *P* for trend 0.05). Elevated serum triglyceride and plasma fasting glucose concentration predicted lower PD risk even after excluding the first 10 years of follow-up. After this exclusion and further adjustment for other components of the metabolic syndrome, a suggestively increased PD risk was observed in overweight individuals (≥25 kg/m^2 vs.<25 kg/m^2, RR = 1.75, 95%CI: 1.00, 3.07, *P* for trend 0.22). Blood pressure, serum HDL cholesterol, or serum total cholesterol carried no prediction of PD risk.

Conclusion: Elevated serum triglyceride and plasma fasting glucose concentrations predict low PD incidence whereas high BMI seems to be suggestively related to an increased PD risk.

1. Introduction

Growing evidence supports an association between increased risk of Alzheimer's disease or dementia and cardiovascular risk factors [1]. In contrast, prospective studies on the association between the components of metabolic syndrome and incidence of Parkinson's disease (PD) have, however, given inconsistent results [2] as well for hypertension [3–6], serum total cholesterol [4,7], diabetes [2,4,8], as for obesity [8–13].

The inconclusive results could be due to many factors such as methodological differences or problems (for example population demographics, exposure information, difficulties in case ascertainment, residual confounding, etc.). One important reason, that has not received much attention, could be that a very long follow-up is needed to account for the potential preclinical disease phase in PD. This affects especially the associations between metabolic syndrome and PD, as it seems that the sympathetic nervous system damage in PD decreases sympathetic activity and thus reduces cardiovascular disease risk factors [14,15].

Apparently, no prospective studies have been published predicting PD incidence by the criterion of the metabolic syndrome. Also more information is needed on the association between individual metabolic factors and PD. The aim of this study was therefore in a representative cohort to predict the incidence of PD by the metabolic syndrome and its components in a prospective study design. In addition, association between total serum

* Corresponding author. National Institute for Health and Welfare, P.O. Box 30, FI-00271 Helsinki, Finland.
E-mail addresses: katri.saaksjarvi@thl.fi (K. Sääksjärvi), paul.knekt@thl.fi (P. Knekt), satu.mannisto@thl.fi (S. Männistö), jukka.lyytinen@hus.fi (J. Lyytinen), markku.heliovaara@thl.fi (M. Heliövaara).

http://dx.doi.org/10.1016/j.parkreldis.2015.07.017
1353-8020/

cholesterol and PD incidence was studied.

2. Methods

2.1. Study population

The Mini-Finland Health Survey was carried out from 1978 to 1980 in 40 areas of Finland, and was based on a stratified two-stage cluster sample (n = 8000) drawn from the population register to represent Finnish adults aged 30 years or over [16]. A total of 7217 individuals (90% of the sample) participated in the survey, which included a health examination. Of these, participants aged 30–79 were included in the present cohort study (n = 7041). Individuals identified as PD cases or reporting use of antipsychotic medication due to psychotic disorders [ICD-10 (International Classification of Diseases) codes F20–F39] were excluded at baseline. Thus, the final study population comprised 6641 individuals. The participants of the Mini-Finland survey participated voluntarily and were fully informed about the study, and the use for medical research was explained to them.

2.2. Assessment of exposure

A health interview and a self-administered questionnaire provided information on education, smoking, alcohol consumption, leisure time exercise, coffee consumption, previous diseases (e.g. diabetes and cardiovascular diseases), and antihypertensive medication at baseline. At the baseline examinations, height and weight were measured and BMI (kg/m^2) was calculated. Casual blood pressure was measured twice with a 1.5 min interval by the auscultatory method. Over-night (at least 11 h) fasting blood samples were taken and stored at −20 °C. Serum HDL cholesterol was analysed using Mg-dextrane sulphate precipitation and serum triglyceride concentration was determined using the fully enzymatic method (Boehringer, Mannheim, Germany). Plasma fasting glucose was determined using a glucose oxidase method (Boehringer, Mannheim, Germany). Serum total cholesterol was determined by a modification of the direct Liebermann–Burchard method without serum-blank subtraction. These were determined a few weeks after the samples were taken. Serum 25-hydroxyvitamin D was determined using radioimmunoassay (DiaSorin, Stillwater, Minnesota) in 2002.

The definition of the metabolic syndrome (MetS) was based on the harmonized definition of the metabolic syndrome [17]. Since the present data did not include information on waist circumference, BMI was used as a proxy measure by replacing the waist circumference category normal with a BMI <25 kg/m^2 and the category large with a BMI ≥25 kg/m^2. However, the correlation between the waist circumference and the BMI was found to be high (r = 0.86) when examined in the Health 2000 data, a representative sample of Finnish adults [18]. The criterion for MetS was the presence of any 3 or more of the following 5 components: BMI ≥25 kg/m^2, elevated mean blood pressure (SBP ≥130 mmHg or DBP ≥85 mmHg or antihypertensive drug treatment), elevated serum triglycerides (≥1.7 mmol/L), reduced serum HDL cholesterol (<1.3 mmol/L in women and <1.0 mmol/L in men), and elevated plasma fasting glucose (≥5.6 mmol/L).

The serum total cholesterol was considered elevated if the concentration was ≥5 mmol/L [19].

2.3. Case ascertainment

PD cases (ICD-10 code G20) were ascertained through the nationwide registry of the Social Insurance Institution of patients receiving medication reimbursement, using a unique personal identity number given to all Finnish citizens. To obtain this allowance for free drug treatment, PD patients must apply for it and attach a certificate from a treating neurologist describing the clinical diagnostic criteria, including symptom history and findings from clinical examinations (stating the presence of resting tremor, bradykinesia and/or muscle rigidity along with other findings). The allowance is granted after inspection of the claim by another neurologist at the Social Insurance Institution. The medication allowance is not granted for patients with, for example, essential tremor, intention tremor, or parkinsonism caused by neuroleptics. A sample of the certificates for PD drug reimbursement and selected hospital records were re-evaluated retrospectively by our study neurologist (JL), and 80% of originally identified PD cases in the register met the criteria [20]. The follow-up time was defined as the number of days from the baseline examination to the dates of PD occurrence, death, or end of follow-up (31.12.2007), whichever came first. During a 30-year follow-up from 1978 to 2007, 89 individuals were identified as PD cases.

2.4. Statistical analysis

The Cox proportional hazards model was used to estimate relative risks (RR) and 95% confidence intervals (CI) for PD according to the categories of the variables of interest; the MetS (no, yes), the five components of MetS [BMI (<25, ≥25), blood pressure (normal, elevated), serum triglycerides (normal, elevated), serum HDL cholesterol (normal, reduced), and plasma fasting glucose (normal, elevated)], and the serum total cholesterol (normal, elevated) (the cut-off values described above). Test for trend was based on the likelihood ratio test by including a continuous variable in the model. Model-adjusted survival functions were estimated for dichotomized variables on serum triglycerides, plasma fasting glucose and BMI (with cut-off points as described above) using predictive margins [21,22].

Three main models were defined. The first model included the variable of interest, age (continuous) and sex. The second model further included the potentially confounding factors of education (<7 years, 7–12 years, >12 years), smoking (never, former smoker, smokes pipe or cigars only or smokes <30 cigarettes/d, smokes ≥30 cigarettes/d), alcohol consumption (0 g/week, 1–99 g/week for women and 1–199 g/week for men, ≥100 g/week for women and ≥200 g/week for men), leisure-time exercise [none (main leisure-time activities do not include physical strain but e.g. reading and watching television), occasional (main leisure-time activities include light physical strain, e.g. gardening, walking outdoors, or occasional exercise as hobby), regular (main leisure-time activities include regular exercise, e.g. running, skiing, athletics, gymnastics)], vitamin D (median classes <40 nmol/L, ≥40 nmol/L) [23] and coffee consumption (0, 1–3, 4–9, ≥10 cups/day) [24]. The correlations between the exposure and confounding factors were rather low, mostly ranging between 0.01 and 0.31. The highest correlations were between age and systolic blood pressure (r 0.55), alcohol consumption and smoking (r 0.38), and age and alcohol consumption (r 0.33). The third model was based on model 2, but with all five components of the metabolic syndrome simultaneously included. The results in these three models did not notably differ, and only the results for models 2 and 3 are presented in the text and tables. Additional analyses with exclusion of the first 10 years of follow-up were performed to examine the effect of the possible preclinical disease phase. Also, secondary analyses with shorter follow-up time (17 years, until 31.12.1994) were performed due to the concern about the long follow-up without repeated measurements on exposures. Interaction analyses could not be performed due to the small number of PD cases. All analyses were carried out using SAS software version 9 (SAS Institute, Inc., Cary, North

Please cite this article in press as: K. Sääksjärvi, et al., Prospective study on the components of metabolic syndrome and the incidence of Parkinson's disease, Parkinsonism and Related Disorders (2015), http://dx.doi.org/10.1016/j.parkreldis.2015.07.017