Appendix S1

SUPPLEMENTARY MATERIAL

Description of methods

All clinical health examinations and all measurements were done at the age of 46 years (S1). The examination included body weight and height, body mass index (BMI), waist and hip circumferences, body index measurements (including body fat mass, fat percentage, muscle mass and visceral fat area), systolic and diastolic blood pressures.

Glucose metabolism was defined by the fasting plasma glucose (FPG) and glycated haemoglobin fraction (HbA1c) levels, and by performing an oral glucose tolerance test (OGTT). Fasting glucose and insulin values were used to calculate fasting indices, Homeostatic Model Assessment for Insuline Resistance (HOMA-IR) and HOMA 2-B-index. Previously diagnosed diabetes was defined according to the self-reported diagnoses and medications, hospital outpatient and inpatient registers and medication registers from the Social Insurance Institution of Finland. The concentration of HbA1c and the concentration of total haemoglobin were measured by immunochemical assay method. Glucose levels were analysed using an enzymatic hexokinase/glucose-6-phosphate dehydrogenase method (both methods: Advia 1800; Siemens Healthcare Diagnostics Inc., Tarrytown, Ny, USA). The samples were analysed in NordLab Oulu, a testing laboratory (T113) accredited by the Finnish Accreditation Service (FINAS) (EN ISO 15189).

Other biological measurements included total serum cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, serum testosterone (T), sex hormone-binding globulin (SHBG) and highly sensitive C-reactive protein (hs-CRP). Free testosterone (FT) was calculated using albumin, SHBG and testosterone concentrations and the equation by Vermeulen et al. (S2). Free androgen index (FAI) was also determined (T/SGBG).

Three CVD risk assessment tools were used: Framingham Risk Score (S3), SCORE (S4) and FINRISK (S5, S6). Fatty liver disease was predicted using a Fatty Liver Index (FLI) algorithm (S7).

Carotid intima-media measurement

To evaluate the presence of possible subclinical cardiovascular disease, specific measures from carotid ultrasound were selected that were assumed to reflect early atherosclerosis. The carotid ultrasound was performed on-line by an experienced cardiologist using the General Electric Vivid E9 device with a 9L-D 2.4/10.0 MHz linear transducer for vascular and a M5S-D 1.5/4.6 MHz sector transducer for cardiovascular imaging (GE Health Medical, Horten, Norway). All the measurements followed the American Society of Echocardiography guidelines valid at the beginning of the study (ASE guidelines) (S8). The mean carotid intima-media thickness (CIMT) was used in the final analysis.

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