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Uterine fibroids and cardiovascular risk

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Uterine fibroids and cardiovascular risk

Running title: Uterine fibroids and cardiovascular risk

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27 **ABSTRACT**

28 **Study question:**

29 Are uterine fibroids associated with increased cardiovascular risk?

30 **Summary answer:**

31 We herein report of an association between increased serum lipids and metabolic syndrome with
32 increased risk of uterine fibroids.

33 **What is known already:**

34 Uterine fibroids are the most common tumour in females. Recent studies suggest similarities in
35 biological disease mechanisms for fibroids and atherosclerosis. Similar risk factors have been
36 associated with both conditions: obesity, hypertension, and abnormal serum lipids. These findings are
37 awaiting confirmation that a population based follow-up study could offer with extensive health
38 examination data collection linked with a national hospital discharge register.

39 **Study design, size, duration:**

40 The Northern Finland Birth Cohort (NFBC1966) is a population-based long-term follow-up study
41 including all children with estimated date of delivery in 1966 in the Northern Finland area. The data were
42 collected from national registries, postal questionnaires and clinical health examinations. All females
43 included in the NFBC 1966 that underwent an extensive clinical health examination at age 46 years
44 (n=3,635) comprised the study population for this study.

45 **Participants/materials, setting, methods:**

46 All females included in the NFBC1966 who were alive and traceable (n=5,118) were invited for the 46-
47 year follow-up study; 3,268 (63.9%) responded, returned the postal questionnaire and attended the
48 clinical examination. Uterine fibroid cases were identified through the national hospital discharge
49 register that has data on disease diagnoses based on WHO ICD-codes. Uterine fibroid codes, ICD-9:
50 218 and ICD-10: D25 were used for case identification. Self-reported fibroid cases were identified
51 through the postal questionnaire.

52 **Main results and the role of chance:**

53 A total of 729 fibroid cases were identified, including 293 based on hospital discharge registries. With
54 adjustment for BMI, parity, education, and current use exogenous hormones the risk of prevalent
55 fibroids rose significantly for every 1 mmol/l increase in LDL (OR=1.13, 95%CI 1.02 to 1.26 for all cases)
56 and triglycerides (OR=1.27, 95%CI 1.09 to 1.49 for all cases). Metabolic syndrome associated with
57 hospital discharge-based fibroid diagnosis (OR= 1.48, 95%CI 1.09 to 2.01). Additionally every 1 unit
58 increase in waist-hip ratio associated with fibroids (OR=1.32, 95% CI 1.10 to 1.57).

59 **Limitations, reasons for caution:**

60 The case ascertainment may present some limitations. There was likely an under-identification of cases
61 and misclassification of some cases as controls; this would have diluted the effects of reported
62 associations. The data analysed were cross-sectional and therefore cause and effect for the
63 associations observed cannot be distinguished.

64 **Wider implications of the findings:**

65 Increased serum lipids and metabolic syndrome are associated with increased risk of uterine fibroids.
66 Along with central obesity these findings add to an increased risk for cardiovascular disease among
67 women with fibroids. These observations may suggest that there are shared predisposing factors
68 underlying both uterine fibroids and adverse metabolic and cardiac disease risk, or that metabolic
69 factors have a role in biological mechanisms underlying fibroid development.

70 **Study funding/competing interests:**

71 This study was supported the Academy of Finland, University Hospital Oulu, University of Oulu, Finland,
72 Northern Finland Health Care Foundation, Duodecim Foundation, ERDF European Regional
73 Development Fund - Well-being and health: Research in the Northern Finland Birth Cohort 1966. The
74 authors declare no conflict of interest.

75 **Keywords:** uterine fibroids, epidemiology, population based birth cohort studies, cardiovascular risk,
76 lipid metabolism, glucose metabolism
77
78
79

Introduction

Uterine fibroids are the most common tumour in females with incidence of nearly 70% by age 50 years (Baird, et al., 2003). Fibroids decrease the quality of life by causing significant morbidity for the women. The related symptoms are heavy and prolonged menstrual bleeding, anaemia secondary to bleeding, pelvic pain and pressure and reduced fertility (Stewart, 2001). Current treatment options for uterine fibroids are limited to hormonal treatments, surgery, and latest the high intensity focused ultrasound (HIFU). All therapies, however, associate with substantial side effects and risks. The mainstream medications, based on the NICE (2013) *Fibroids* guidelines (levonorgestrel, progestogen, combined oral contraceptives, GnRH, ulipristal acetate, tranexamic acid and NSAIDs) focus on easing the symptoms rather than targeting the specific molecular disease mechanisms. The significant surgical need for fibroid treatment is well reflected by the fact that uterine fibroids are the primary indication for hysterectomy (Brummer, et al., 2009, Farquhar and Steiner, 2002). Given all this, uterine fibroids cause significant financial burden for the society (Soliman, et al., 2015) with an annual cost of 52.7 million euros in UK (Fernandez, et al., 2009) alone. The field of uterine fibroid biology has achieved crucial breakthrough discoveries through next-generation genetic studies in the very recent past by the discovery of mutations in MED12, which is a subunit of the mediator complex that regulates global and gene-specific transcription. The mutation has been recognised with a frequency of 70% of uterine fibroids (Makinen, et al., 2011). Yet the fundamental fibroid development mechanisms are still to be revealed.

Recent studies have indicated an association between uterine fibroids and several cardiovascular disease (CVD) risk factors such as hypertension, obesity, abnormal serum lipids and carotid intima-media (CIM) thickness (Aksoy, et al., 2014, Boynton-Jarrett, et al., 2005, He, et al., 2013, Luoto, 2002, Luoto, et al., 2001, Sadlonova, et al., 2008, Silver, et al., 2005, Summers, et al., 1971, Templeman, et al., 2009). The largest cohort study on fibroids, the Nurses' Health Study II (NHS II) provides evidence for association of both hypertension (Boynton-Jarrett, Rich-Edwards, Malspeis, Missmer and Wright, 2005) and obesity (Marshall, et al., 1998) with increased risk of fibroids. Other studies have had limitations regarding case definition, study population, sample

size, or reproducibility. Comprehensively assessed study on metabolic and cardiovascular risk profiles and their association to uterine fibroids would bring enlightenment to this study field. The Northern Finland Birth Cohort 1966 (NFBC1966) is a prospective population-based study comprising more than 12,000 participants with follow-up from birth to, currently, age 46 years. The present study utilizes extensive health examination data collected from women at age 46 years linked with national hospital discharge registers to evaluate the association between uterine fibroids and several CVD risk factors and metabolic factors. Measures for body mass index (BMI), waist and hip circumferences, body composition, oral glucose tolerance, International Diabetes Federation (IDF)-defined metabolic syndrome, serum lipids, sex hormones and high sensitivity C-reactive protein (hs-CRP), brachial blood pressure, and fatty liver index (FLI) were assessed. In addition, the present study investigated patient-specific CVD risk assessment scores (Framingham Risk Score and SCORE) to evaluate the metabolic risk for future cardiovascular events in women with uterine fibroids.

128 **Methods**

129

130 **Study population**

131 The study population derives from the prospective Northern Finland Birth Cohort
132 1966 (NFBC1966), comprising 96.3% of all estimated births in the two northernmost
133 provinces of Finland (Oulu and Lapland) during the year 1966. NFBC1966 originally
134 included 12,068 mothers who gave birth to 12,231 live born children (173 stillbirths),
135 of whom 5,889 were females, all Caucasian. Data collection begun at gestational
136 week 24 and so far data has been collected at ages 1, 14, 31 and 46 years. The women
137 who were alive and whose contact information was traceable (n = 5,118) received an
138 invitation for the 46-year follow-up study. In addition to a postal questionnaire,
139 women were invited to a clinical health examination. 3,733 (72.9%) responded and
140 returned the questionnaire and 3,268 (63.9%) attended the clinical examination and
141 gave blood samples.

142 **Ethics Statement**

143 The Ethical Committee of the Northern Ostrobothnia Hospital District approved the
144 study, which followed the principles of the Declaration of Helsinki. The participants
145 took part on a voluntary basis and signed their informed consent. The data were
146 handled on a group level only, the personal information being replaced by
147 identification codes.

148

149 **Ascertainment of uterine fibroid**

150 Uterine fibroid cases were identified in the cohort through national outpatient and
151 inpatient hospital discharge register that has data on disease diagnoses identified by
152 WHO ICD disease codes. The national hospital discharge register includes ICD-codes
153 and dates for each hospital visit, and since year 1968 this data has been regularly
154 collected for the cohort population database. In the Finnish Healthcare system ICD-
155 codes are used primarily for clinical diagnoses purposes, and secondly for municipal
156 billing purposes. The ICD-codes are set by the clinical doctor who is in charge of
157 discharging the patient, and the codes are chosen based on their clinical relevance for
158 each hospital visit. Thus the disease diagnoses data is considered accurate and reliable.
159 Uterine fibroid codes, ICD-9: 218 and ICD-10: D25 were used for case identification.
160 Earlier used ICD-8 codes have been converted to ICD-9 codes and thus were included.

161 This case ascertainment method identifies those fibroid patients who had required
 162 referral from primary health care or private sector to clinical review in specialty care;
 163 usually for consideration of surgical treatment or medical treatment after first and/or
 164 second line treatments have been unsuccessful. So forth those cases have been
 165 identified to whom fibroid diagnosis was of clinical significance with substantial
 166 symptoms. The fibroid diagnosis had been confirmed by a clinician, based either on
 167 clinical examination, imaging (ultrasonography, or other such as MRI or CT) or
 168 surgery.

169 Additionally, self-reported fibroid cases were identified through the postal
 170 questionnaire collected at age 46 years with a question “Have you been diagnosed
 171 with uterine fibroids? If yes, at what age? If yes, was the diagnosis confirmed by
 172 gynaecological examination / ultrasonography / surgical operation (laparoscopy or
 173 laparotomy)?” Only cases with self-reported confirmation by either ultrasonography
 174 or surgical operation were recognised. A validation study was performed to assess
 175 reliability of the self-reported fibroid cases and 79% (n=231/293) of the self-identified
 176 fibroids were confirmed by ICD-codes. Finally, the control group was formed of the
 177 rest cohort population (Figure 1).

178

179 **Anthropometric measurements**

180 All clinical health examinations took place and all measurements were taken at age 46
 181 years. Body weight was measured with digital scale, which was calibrated regularly.
 182 Height was measured two times (mean of the two measurements was used) by using
 183 standard and calibrated stadiometer. Body mass index (BMI) was calculated as the
 184 ratio of weight and height squared. Waist and hip circumferences were measured
 185 twice (mean of the two measurements was used) and the waist-hip ratio (WHR) was
 186 assessed as the ratio between circumferences of the waist (at the level midway
 187 between lowest rib margin and the iliac crest) and the hip (at the widest trochanters).
 188 Body fat mass, fat percentage, muscle mass and visceral fat area were measured by
 189 InBody 720 bioelectrical impedance analyser (Biospace Co., Ltd., Seoul, Korea). All
 190 measurements were done after overnight (12h) fasting period.

191

192 **Cardiovascular measurements**

193 Systolic and diastolic blood pressure was measured three times with 1 min interval
 194 after 15min of rest on the right arm of the seated participants using an automated

195 oscillometric blood pressure device and appropriately sized cuff (Omron Digital
196 Automatic Blood Pressure Monitor Model M10-IT). Finally, the mean of two lowest
197 systolic values and their diastolic values was used in the analyses.

198

199 **Oral glucose tolerance test and diabetes**

200 A two-hour oral glucose tolerance test (OGTT) was performed after overnight (12
201 hour) fasting period. Exclusion criteria were medication for diabetes or just before test
202 measured capillary blood glucose level >8.0 mmol/l. Both serum insulin and plasma
203 glucose were measured at baseline and 30, 60 and 120 minutes after 75g glucose
204 intake. Glucose tolerance status was classified according to World Health
205 Organization (WHO) criteria: 1) normal glucose tolerance (NGT) was defined as
206 having fasting plasma glucose (FPG) level <6.1 mmol/l and 2-hour glucose level <7.8
207 mmol/l, 2) impaired fasting glucose (IFG) as having FPG level 6.1-6.9 mmol/l and 2-
208 hour glucose level <7.8 mmol/l, 3) impaired glucose tolerance (IGT) as having FPG
209 level <7.0 mmol/l and 2-hour glucose level 7.8-11.0 mmol/l, and 4) screen detected
210 diabetes mellitus (scDM) as having FPG level ≥ 7.0 mmol/l and/or 2-hour glucose
211 level ≥ 11.1 mmol/l. Fasting glucose and insulin values were used to calculate fasting
212 indices: HOMA-IR index (Homeostasis Model Assessment – insulin resistance) ($\text{FPG} \times \text{FSI} / 22.5$),
213 HOMA2- β index (Homeostasis Model Assessment – beta-cell function)
214 ($(20 \times \text{FSI}) / ((\text{FPG} - 3.5) \times 100)$) and QUICKI index (Quantitative Insulin Sensitivity
215 Check Index) ($1 / (\log \text{FBG} + \log \text{FPI})$). OGTT glucose and insulin values were used
216 to calculate insulin and glucose area under curve (glucose-AUC and insulin-AUC),
217 several indices for insulin sensitivity: Matsuda index (ISI) ($10\,000 \times ((\text{FPG} \times \text{FSI}) \times$
218 $((\text{FPG} + 30\text{min PG} + 60\text{min PG} + 120\text{min PG}) / 4) \times ((\text{FSI} + 30\text{min SI} + 60\text{min SI} +$
219 $120\text{min SI}) / 4))$), Belfiore index ($2 / (((0.5 \times \text{FPG}) + 60\text{min mean PG} + (0.5 \times 120\text{min}$
220 $\text{PG}) \times (((0.5 \times \text{FPG}) + 60\text{min PI} + (0.5 \times 120\text{min PI})) / 638) + 1))$), and Gutt index
221 ($(75000 + (\text{FPG} - 120\text{min PG} \times 0.19 \times \text{weight [kg]} / 120) / ((\text{FPG} + 120\text{min PG} / 2) /$
222 $\text{LOG}_{10} ((\text{FPI} + 120\text{min PI}) / 2))$ (Belfiore, et al., 1998, Gutt, et al., 2000, Katz, et al.,
223 2000, Matsuda and DeFronzo, 1999, Matthews, et al., 1985). Previously known
224 diabetes (prDM) was defined according to self-reported diagnoses and medications,
225 hospital outpatient and inpatient registers and medication registers from Social
226 Insurance Institution of Finland.

227

228 **Other biochemical measurements**

229 Blood samples were taken after an overnight fasting period, centrifuged immediately
230 and stored firstly at -20°C and later at -80°C . All blood samples were analysed in
231 the laboratory of the University Hospital of Oulu according to a standardized protocol.
232 Serum total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein
233 (LDL), and triglycerides were determined using an enzymatic assay method (Advia
234 1800; Siemens Healthcare Diagnostics Inc., Tarrytown, Ny, USA). Serum samples for
235 testosterone (T) were analysed using Agilent triple quadrupole 6410 LC/MS equipped
236 with electrospray ionisation source operating with positive-ion mode (Agilent
237 Technologies, Wilmington, DE, USA). Multiple reaction monitoring was used to
238 quantify testosterone by d3-testosterone with the following transitions: m/z 289.2 to
239 97 and 289.2 to 109 for testosterone and 292.2 to 97 and 292.2 to 109 for d3-
240 testosterone. The intra-assay CVs of the method were 5.3%, 1.6 % and 1.2 % for
241 testosterone at 0.6, 6.6 and 27.7 nmol/l, respectively. The interassay CVs were 5.3%,
242 4.2% and 1.0% for the respective concentrations. Serum sex hormone-binding
243 globulin (SHBG) was analyzed by chemiluminometric immunoassay (Immulite 2000,
244 Siemens Healthcare Diagnostica Inc., Llanberis, UK). High sensitivity C-reactive
245 protein (hs-CRP) was analyzed by an immune nephelometric assay (BN ProSpec,
246 Siemens Healthcare Diagnostics Inc., Newark, DE, USA)

247

248 **CVD risk assessment scoring**

249 Two CVD risk assessment tools were used, Framingham Risk Score (D'Agostino, et
250 al., 2008) and SCORE (Conroy, et al., 2003). The Framingham Risk Score estimates a
251 10-year risk of developing coronary heart disease, cerebrovascular events, peripheral
252 artery disease or heart failure. It bases its risk-percentage result on the following
253 factors: gender, age, smoking, total cholesterol, HDL-cholesterol, systolic blood
254 pressure, requiring treatment for raised blood pressure, and diabetes. As a result the
255 Framingham risk assessment tool reports points ranging from ≤ -2 to ≥ 21 that refer to
256 a risk percentage ranging from $<1\%$ to $>30\%$ (D'Agostino, Vasan, Pencina, Wolf,
257 Cobain, Massaro and Kannel, 2008). The SCORE estimates a 10-year risk of fatal
258 cardiovascular disease on the basis of gender, age, smoking, total cholesterol and
259 systolic blood pressure. It results risk percentages ranging from $<1\%$ to $\geq 15\%$
260 (Conroy, Pyorala, Fitzgerald, Sans, Menotti, De Backer, De Bacquer, Ducimetiere,

261 Jousilahti, Keil, Njolstad, Oganov, Thomsen, Tunstall-Pedoe, Tverdal, Wedel,
262 Whincup, Wilhelmsen, Graham and group, 2003).

263

264 **Metabolic syndrome**

265 Metabolic syndrome was assessed according to the International Diabetes Federation
266 (IDF) Worldwide Definition (Alberti, et al., 2006), which is a unified working
267 diagnostic tool for the metabolic syndrome. The tool results with yes or no for
268 metabolic syndrome based on central obesity measured by waist circumference
269 (≥ 80 cm) and any two of the following: raised triglycerides (≥ 1.7 mmol/l or specific
270 treatment for this lipid abnormality), reduced HDL (< 1.29 mmol/l or specific
271 treatment for this lipid abnormality), raised blood pressure (systolic ≥ 130 mmHg or
272 diastolic ≥ 85 mmHg or treatment of previously diagnosed hypertension), raised fasting
273 plasma glucose (≥ 5.6 mmol/l or previously diagnosed type 2 diabetes).

274

275 **Fatty liver index**

276 Fatty liver disease is strongly associated to obesity and it can be predicted using a
277 fatty liver index (FLI) algorithm, which is based on BMI, central obesity measured by
278 waist circumference, triglyceride and gamma-glutamyl-transferase (GGT) levels
279 (Bedogni, et al., 2006). FLI is calculated as: $FLI = (e^{0.953 \cdot \log_e(\text{triglycerides})} +$
280 $0.139 \cdot \text{BMI} + 0.718 \cdot \log_e(\text{ggt}) + 0.053 \cdot \text{waist circumference} - 15.745) / (1 + e^{0.953 \cdot \log_e(\text{triglycerides})} +$
281 $0.139 \cdot \text{BMI} + 0.718 \cdot \log_e(\text{ggt}) + 0.053 \cdot \text{waist circumference} - 15.745) * 100$. FLI
282 varies between 0 and 100, with cut offs at 30 and 60; score < 30 rules out fatty liver
283 and a score ≥ 60 is considered a strong predictor for fatty liver.

285

286 **Confounders**

287 Data on parity was obtained from the postal questionnaire and national birth register.
288 Exogenous hormone use, both lifetime and current, and self-reported polycystic ovary
289 syndrome (PCOS) was obtained from the postal questionnaire. Menopausal status was
290 determined by a question on climacteric symptoms on the postal questionnaire.
291 Women reported their lifetime education level, which was categorised as basic,
292 secondary, or tertiary. Socioeconomic status was again determined by questions on
293 the postal questionnaire and categorised as entrepreneur, higher administrative, lower

294 administrative, blue-collar worker, or other. Women reported their leisure-time
295 physical activity level in the questionnaire before health examinations. The four
296 categories were named inactive, lightly active, active, or very active. Smoking history
297 and present status was inquired and results reported as non-smoker, former smoker
298 more than 6 months ago, former smoker less than 6 months ago, or current smoker.
299 Women reported their alcohol consumption and the four categories were named non-
300 user, light user, moderate user, or heavy user.

301

302 **Statistical methods**

303 Distributions of continuous variables were expressed as mean \pm standard deviation
304 (SD), and categorical variables as numbers and percentage of proportions. The χ^2 -
305 test and Mann-Whitney U test were used to study associations between uterine fibroid
306 cases and controls with cardiovascular risk factors.

307 Logistic regression analysis was used to examine associations between uterine fibroid
308 cases and controls with known cardiovascular risk factors. The analysis was first
309 performed for all fibroid cases and then for ICD-code identified cases. BMI, parity,
310 education and current use exogenous hormones were used as potential confounding
311 factors in the analyses (Table I). P-value <0.05 was considered statistically significant.
312 Statistical analyses were conducted using the free software package R 3.1.0.

313 Results

314
315 We identified 729 uterine fibroid cases in the NFBC1966 by year 2012 for this study.
316 Of these cases 293 were identified through WHO ICD disease codes for uterine
317 fibroids. The rest of the cohort population formed the control group (n = 2,906)
318 (Figure 1). Figure 2 presents the overall ICD-code based uterine fibroid incidence in
319 the cohort. This includes all women who participated in either the postal
320 questionnaires or the clinical examinations. Cumulative incidence was 7.7%. The
321 number of newly detected cases starts to increase after age 41 years, and by age 46
322 years there were a total of 395 ICD-code identified fibroid cases in the cohort. The
323 mean age of fibroid diagnosis was 37.3 years (median 40.0, SD 7.1, range 13-47), and
324 for the ICD-code confirmed fibroid cases 40.2 years (median 42 years, SD 5.3, range
325 23-46).

326 Confounders

327 Women with uterine fibroids had significantly lower parity than women without
328 fibroids (mean 1.8 SD 1.7 vs. 2.2 SD 1.8, $P<0.001$) (Table I). There were significant
329 differences in body size among women with and without uterine fibroids. Women
330 with fibroids were more frequently overweight or obese (35.4% and 21.8% vs. 31.6%
331 and 21.4%, $P=0.04$). There were no differences in lifetime use exogenous hormones,
332 but current use differed in hormonal replacement therapy for all fibroids (3.8% vs.
333 2.4%, $P=0.04$). There were no differences in polycystic ovary syndrome or
334 menopausal status defined by experienced climacteric symptoms. Again, there were
335 no significant differences in regards of cigarette smoking, alcohol use, or physical
336 activity. Women with fibroids had a lower lifetime education level (basic 3.8% and
337 tertiary 39.8% vs. 2.0% and 41.6%, $P=0.012$), but they did not differ in their
338 socioeconomic status when compared to women without fibroids (Table I). These
339 results defined the adjustment models for parity, education level, BMI, and current
340 use exogenous hormones as applied in the analyses.

341

342 Anthropometrics

343
344 With logistic regression analysis, the odds ratio of uterine fibroid diagnosis (all cases,
345 and WHO ICD-code identified cases) according to several known cardiovascular
346 disease risk factors was estimated. With adjustment for parity, education, BMI, and

current use exogenous hormones the risk of prevalent fibroids rose significantly for every 1cm increase in waist circumference (OR=1.02, 95%CI 1.00 to 1.04) (Table II). Also every unit increase in WHR associated with fibroids (OR=1.32, 95%CI 1.10 to 1.57) (Table II). However, increase in body composition: fat percentage, fat mass, skeletal muscle mass, visceral fat area, did not show association to fibroids (Table II). The results for ICD-code confirmed cases were congruent (Table II).

Glucose metabolism

The 2-hour OGTT results suggest a positive association between glucose metabolism and uterine fibroid risk. This is shown in insulin levels at 60 minutes when adjusting for parity and education (All uterine fibroid cases: OR=1.02 95%CI 1.00 to 1.04) and in glucose levels at 30 minutes (ICD-code confirmed cases: OR=1.13 95%CI 1.03 to 1.24) (Table III). Interestingly, glucose tolerance results meeting the criteria of IFG showed a significant association among the ICD-code confirmed cases only in the fully adjusted model (OR=1.81 95%CI 0.98 to 3.14) (Table III).

Lipid metabolism

Serum lipids associated with uterine fibroids independent of parity, education, BMI, and current use exogenous hormones. For every 1mmol/l increase in LDL and triglycerides the risk of prevalent fibroids rose significantly (OR=1.13 95%CI 1.02 to 1.26 and OR=1.27 95%CI 1.09 to 1.49) (Table IV). The associations were stronger for hospital discharge defined fibroid cases (OR=1.22 95%CI 1.05 to 1.42 and OR=1.37 95%CI 1.11 to 1.68). Additionally for these cases, every 1mmol/l increase in total cholesterol associated with fibroids (OR=1.21 95%CI 1.05 to 1.41). These associations were not altered when the model was additionally adjusted for polycystic ovary syndrome.

Blood pressure, metabolic syndrome and cardiovascular risk scores

Blood pressure measured at age 46 years did not show association with uterine fibroid risk (Table IV). IDF defined metabolic syndrome associated with hospital discharge based fibroid diagnosis significantly, independent of parity, education, BMI, and current use exogenous hormones (OR=1.48 95%CI 1.09 to 2.01). The CVD risk assessment scoring was performed by using two widely used tools; Framingham CVD

380 risk score and SCORE. The analysis did not show significant association with fibroids
381 according to either CVD risk assessment scores, in any of the adjustment models.

382

383 **Liver function and chronic inflammation**

384 Fatty liver index (FLI) was not associated with uterine fibroids in this analysis. When
385 adjusting for parity and education, hs-CRP 1-3 mg/l associated with hospital
386 discharge based fibroid diagnosis (OR=1.35 95%CI 1.01 to 1.80) (Table IV), but this
387 association became non-significant after adjusting additionally for BMI and current
388 use exogenous hormones (Table IV).

389

390 **Sex hormones**

391 With the full adjustment model, no association was observed for SHBG (Table IV).
392 However, every 1 nmol/l increase in serum total testosterone associated with ICD-
393 code confirmed fibroid cases (OR=0.60 95%CI 0.40 to 0.89) (Table IV).

394

395 **Discussion**

396
 397 In this population-based birth cohort study we report unfavourable alterations in
 398 several well-documented cardiovascular disease risk factors in women diagnosed with
 399 uterine fibroids. At the age of 46 years, increased serum total cholesterol, LDL and
 400 triglyceride levels were associated with increased risk of fibroids. The odds ratios
 401 were higher among women with hospital discharge based WHO ICD-code for fibroid
 402 diagnosis, suggesting stronger associations of the tested risk factors among women
 403 with more severe fibroid related symptoms and thus large or multiple fibroids.
 404 Additionally, impaired glucose tolerance and metabolic syndrome were associated
 405 with fibroid risk.

406

407 **Strengths and weaknesses of the study**

408 Our analyses were conducted in a large population based cohort with accurate data on
 409 medical diagnoses at specialty care, vast clinical examinations and extensive
 410 questionnaires. The cohort database has precise data on body size and an extensive
 411 range of assayed metabolic biochemical markers. The strength of our study is that we
 412 were able to analyze all CVD risk factors simultaneously in the same study population,
 413 in the same time period.

414

415 The case ascertainment may present some limitations. There was likely an under-
 416 ascertainment of cases and misclassification of some cases as controls due to the fact
 417 that uterine fibroids may present as asymptomatic and thus remain undiagnosed. This
 418 would have diluted the effects of reported associations. The incidence of fibroids in
 419 this study was 20.1% (729/3635) when considering all cases, and 8.1% (293/3635) of
 420 ICD-code identified cases, whereas the overall ICD-code based incidence in the
 421 cohort, when including all women despite their participation to the clinical
 422 examinations, was 7.7%. Indeed there is a discrepancy when comparing this figure to
 423 the reported cumulative incidence among White women in their late 40s by Baird
 424 2003; ~70% in ultrasound screened study population and 35% in clinically relevant
 425 cases. There are no comparable figures for Finnish population, but an ultrasound
 426 screening study presents a fibroid prevalence for Swedish women aged 33 to 40 years
 427 to be 7.8% (Borgfeldt and Andolf, 2000), which is more in proportion to our findings.
 428 Age of the cohort at the time of clinical examinations was not ideal for cardiovascular

429 risk assesment, as age is the strongest risk factor for cardiovascular disease and the
430 risk starts to rise significantly after the age of 60 years (Tuomilehto, 2004). The data
431 analysed were cross-sectional and therefore cause and effect for the associations
432 observed cannot be distinguished.

433

434 **Comparison to other studies**

435

436 The association between obese body size and uterine fibroids has been confirmed by
437 many studies, although not all studies agree (Table V). In the previous studies body
438 size has been determined by calculating BMI and the results are fairly consistent; data
439 arising from the NHS II with 2,967 identified fibroid cases shows increased risk of
440 fibroids with increasing adult BMI (Marshall, Spiegelman, Manson, Goldman,
441 Barbieri, Stampfer, Willett and Hunter, 1998). Furthermore, central obesity as
442 measured by WHR has been associated with increased risk of fibroids (Sato, et al.,
443 1998, Wise, et al., 2005). Our study confirms the association, as increase in waist
444 circumference and WHR was associated with an increased risk of fibroids. Other
445 adiposity traits (visceral fat or gynecoid pattern fat accumulation), examined through
446 body fat distribution using bioelectrical impedance analysis, did not show association.

447

448 Lipid metabolism in women with uterine fibroids has been analyzed in only few
449 studies and the results are conflicting (Table V). All studies are case-control settings
450 with small sample sizes. In the present study the lipid levels were assessed at the same
451 age for all cohort participants showing a positive association between LDL and
452 triglycerides and risk of fibroids. The unfavourable trend of serum lipid levels seems
453 to be independently associated with fibroids, as when adjusting for parity, education
454 and BMI the results remain statistically significant.

455

456 Published data on the association between glucose metabolism and uterine fibroids is
457 limited. The association has been analysed using mainly self-reported diabetes
458 diagnosis, but also with fasting glucose levels, fasting insulin levels and short insulin
459 tolerance test (Table V). No clear association has been documented in these studies
460 between changes in glucose metabolism and uterine fibroids. The present study
461 analyzed the association with a vast set of glucose metabolism tests and indices, again
462 at the same age for all cohort participants. Women with ICD-code confirmed fibroids

463 showed association to impaired fasting glycemia (IFG), which refers to constant
464 elevation of fasting plasma glucose levels. It can progress to more severe forms of
465 glucose intolerance and further on to diabetes, and thus is considered as a pre-diabetic
466 state (Nichols, et al., 2007). Additionally, the ICD-code confirmed fibroid cases
467 showed association to IDF-defined metabolic syndrome, clustering the effects of
468 several metabolic traits to have association to fibroids, and infer of adverse
469 cardiovascular events, which is the main adverse outcome of metabolic syndrome
470 (DeFronzo and Abdul-Ghani, 2011, Mottillo, et al., 2010).

471

472 There is evidence that hypertension and uterine fibroids are associated. The relation
473 has been shown in many studies, but also suggestion of no association has been
474 published (Table V). However, the NHS II, which is the largest study on fibroids by
475 to date, offers strong evidence on the association and reports every 10 mmHg increase
476 in diastolic blood pressure increased the risk of fibroids by 8% among non-users and
477 10% among users of antihypertensive medications (Boynton-Jarrett, Rich-Edwards,
478 Malspeis, Missmer and Wright, 2005). Our analyses of the NFBC1966 cohort did not
479 support an association between uterine fibroids and hypertension. One reason for this
480 may be the relatively young age of the cohort.

481

482 **Potential mechanisms**

483 First identifications of possible underlying atherosclerotic mechanisms in uterine
484 fibroid development arise from studies performed in the 1970s, when fibroid tissue
485 and atherosclerotic plaque were recognised to have similarities in growth behaviour as
486 they both become fibrotic and calcified (Moss and Benditt, 1975). Further suggestions
487 on atherosclerotic mechanisms arise from notifications of lipid accumulation in
488 myometrial smooth muscle cells in women with pregnancy related hypertension
489 (Haust, et al., 1977), vascular endothelial and myometrial smooth muscle cells seem
490 to react similarly to injury and promote monoclonal expansion of smooth muscle cells
491 in the uterine wall (Cramer, et al., 1995). Monoclonal theory of origin is another
492 shared similarity of these two phenomenons (Andreassi, et al., 2000, Benditt and
493 Benditt, 1973, Hashimoto, et al., 1995, Mashal, et al., 1994).

494 Obesity is associated with different grades of insulin resistance, which is a substantial
495 underlying key process in the development of cardio-metabolic disorders. Central
496 obesity in particular raises the risk for development of metabolic complications, with

497 mounting evidence that not only visceral adipose tissue, but also subcutaneous
498 adipose tissue has a significant impact on the process (Patel and Abate, 2013). In fact,
499 fat distribution in obese premenopausal women is more often characterised with
500 excess subcutaneous fat, but changes in menopause transition to visceral fat
501 accumulation (Toth, et al., 2000). In the first phase of insulin resistance,
502 hyperinsulinemia increases the hepatic synthesis and activity of insulin-like growth
503 factors, such as IGF-I. Insulin resistance seems to play role in uterine fibroid
504 development, as IGF-I may act to promote fibroid growth in an autocrine/paracrine
505 fashion. IGF-I receptors are increased in fibroid tissue compared to myometrium
506 (Chandrasekhar, et al., 1992), and the levels of IGF-I peptide, IGF-I mRNA and IGF-
507 II mRNA are also elevated (Englund, et al., 2000, van der Ven, et al., 1994,
508 Vollenhoven, et al., 1993). A recent study on experimental mouse model reported of
509 induced insulin resistance and administration of oestrogen and progesterone hormones
510 to promote uterine smooth muscle growth, where insulin resistance had an enhancing
511 effect on the steroid hormone stimulation (Hou, et al., 2015). The authors suggest that
512 this might imply of a possible effect of insulin resistance in the development of
513 uterine fibroids. Again, an association study on fibroid tumor size across extended
514 candidate chromosomal regions for uterine fibroids resulted with a sole significant
515 variant in *SORCS2* (sortilin-related VPS10 domain containing receptor 2) gene
516 (Aissani, et al., 2015), which is also a strong candidate gene for circulating IGF-I and
517 IGFBP-3 (Kaplan, et al., 2011).

518 Adding these observations together, it can be proposed that simultaneous and alike
519 disease mechanisms occur in both myometrial smooth muscle and vascular
520 endothelial cells, that would initially be provoked by unfavourable metabolic
521 circumstances. Genes encoding mediator complex have been associated with both
522 uterine fibroids and metabolic syndrome (Makinen, Mehine, Tolvanen, Kaasinen, Li,
523 Lehtonen, Gentile, Yan, Enge, Taipale, Aavikko, Katainen, Virolainen, Bohling,
524 Koski, Launonen, Sjoberg, Taipale, Vahteristo and Aaltonen, 2011, Schiano, et al.,
525 2014). Exploring the biological pathways involving mediator subunits is one way of
526 investigating the common biology between these traits.

527

528 **Conclusions**

529 **Our study provides evidence for uterine fibroids and outcomes that are also associated**
530 **with cardiovascular disease.** According to this large birth cohort study, unfavourable

531 lipid and glucose metabolism, and metabolic syndrome are associated with increased
532 risk for uterine fibroid diagnosis. Along with central obesity these associating factors
533 accumulate to increased risk for cardiovascular disease among women with uterine
534 fibroids. In conclusion, the observed associations may suggest that there are shared
535 predisposing factors underlying both uterine fibroids and adverse metabolic and
536 cardiac disease risk, or that metabolic factors have a role in biological mechanisms
537 underlying fibroid development. However, the causality cannot be determined by a
538 cross-sectional study as ours, and therefore longitudinal prospective studies are
539 needed to further investigate the underlying biological mechanisms in fibroid
540 development.
541
542

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547
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549 proposed the hypothesis. OU, JA, JJ, SKK, KZ, IJ, MR and HM conceived and
550 designed the study. JA, KP, AR, MRJ, TP, SKK and KZ obtained funding. OU, JA, JJ,
551 KP, AR, MRJ, TP, SKK and HM provided study materials and collected and collated
552 data. JJ did the statistical analysis. OU, JA, JJ, TP and HM analyzed and interpreted
553 the data. OU and JA made initial drafts of tables and figures. OU drafted the
554 manuscript. JA, JJ, TP, KZ, IJ, MR and HM critically revised the manuscript for
555 important intellectual content. All authors read and approved the final version of the
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557

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563

564 **Conflict of interest:** The authors declare no conflicts of interest regarding this study.

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709

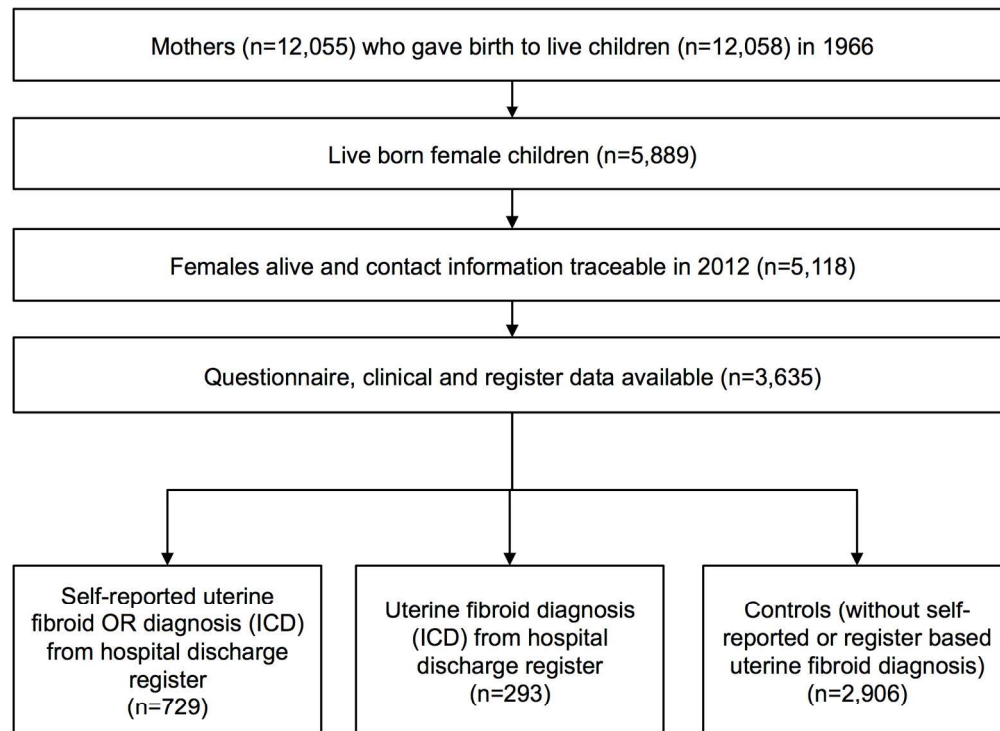


Figure 1 Participants of the uterine fibroid and cardiovascular risk NFBC1966 study.

Participants of the uterine fibroid and cardiovascular risk NFBC1966 study.

166x148mm (300 x 300 DPI)

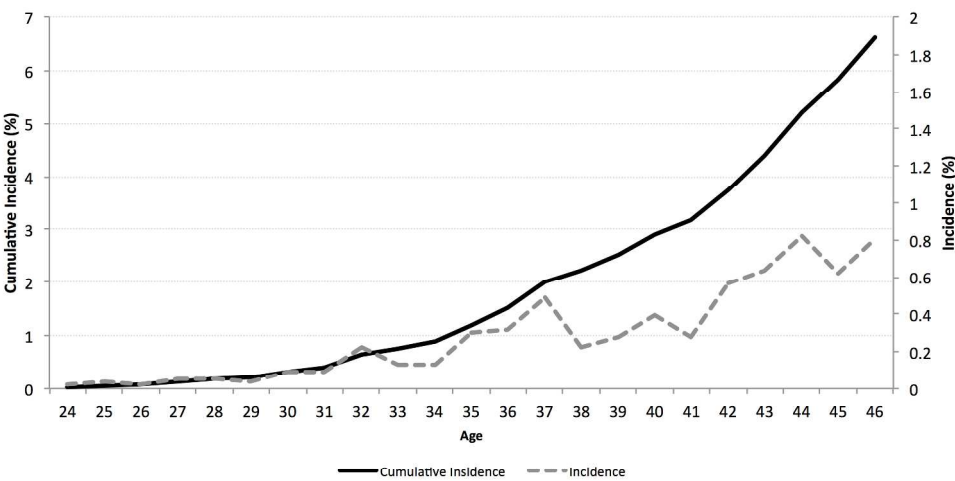


Figure 2 Uterine fibroid incidence in the NFBC1966. Cases were identified through the national hospital discharge register based on WHO ICD-codes for uterine fibroids (ICD-9: 218 and ICD-10: D25, ICD-8 converted to ICD-9).

Uterine fibroid incidence in the NFBC1966. Cases were identified through the national hospital discharge register based on WHO ICD-codes for uterine fibroids (ICD-9: 218 and ICD-10: D25, ICD-8 converted to ICD-9).

244x138mm (300 x 300 DPI)

Table 1 | Characteristics of the NFBC 1966 study population at 46 years in women with and without uterine fibroids. Data are % (n) of population unless stated otherwise.

Characteristics	Percent (N)		p*
	All uterine fibroid cases (n=729)	Controls (n=2906)	
Parity, mean (SD)	1.8 (1.7)	2.2 (1.8)	<0.001
BMI			
Mean, kg/m ² (SD)	26.7 (5.3)	26.5 (5.4)	0.06
Underweight <18.5	0.3 (2)	1.1 (33)	0.04
Normal 18.5-24.9	42.6 (309)	45.9 (1331)	
Overweight 25.0-29.9	35.4 (257)	31.6 (915)	
Obese ≥30.0	21.8 (158)	21.4 (621)	
Lifetime use exogenous hormones	88.7 (637)	89.8 (2603)	0.44
Current use exogenous hormones			
Combined contraceptive	4.4 (32)	5.4 (157)	0.30
Hormonal replacement therapy	3.8 (28)	2.4 (60)	0.04
Polycystic ovary syndrome	6.3 (45)	4.6 (131)	0.06
Menopausal status			
Postmenopausal	33.5 (241)	31.7 (919)	0.37
Premenopausal	66.5 (478)	68.3 (1980)	
Cigarette smoking			
Non-smoker	58.0 (412)	56.5 (1631)	0.85
Former smoker > 6 months ago	20.0 (142)	21.4 (617)	
Former smoker < 6 months ago	1.7 (12)	1.8 (53)	
Current smoker	20.3 (144)	20.2 (584)	
Alcohol use			
Non-user	10.7 (77)	11.7 (338)	0.84
Light user	82.5 (594)	81.7 (2369)	
Moderate user	2.9 (21)	3.2 (92)	
Heavy user	3.9 (28)	3.5 (102)	
Physical activity			
Inactive	20.2 (145)	21.9 (635)	0.50
Lightly active	43.7 (313)	41.0 (1185)	
Active	34.9 (250)	35.5 (1026)	
Very active	1.3 (9)	1.6 (47)	
Education			
Basic	3.8 (28)	2.0 (58)	0.01
Secondary	56.4 (411)	56.4 (1638)	
Tertiary	39.8 (290)	41.6 (1210)	
Socioeconomic status			
Entrepreneur	9.5 (67)	8.8 (246)	0.79
Higher administrative	17.6 (124)	16.7 (470)	
Lower administrative	22.0 (155)	21.0 (590)	
Blue-collar worker	44.7 (314)	47.2 (1324)	
Other	6.1 (43)	6.3 (178)	
	ICD-code identified cases (n=293)	Controls (n=2906)	
Parity, mean (SD)	1.7 (1.4)	2.2 (1.8)	<0.001
BMI			
Mean, kg/m ² (SD)	27.3 (5.9)	26.5 (5.4)	0.01
Underweight <18.5	0.0 (0)	1.1 (33)	0.01
Normal 18.5-24.9	37.5 (109)	45.9 (1331)	

Overweight 25.0-29.9	37.8 (110)	31.6 (915)	
Obese >30.0	24.7 (72)	21.4 (621)	
Lifetime use exogenous hormones	87.3 (248)	89.8 (2603)	0.23
Current use exogenous hormones			
Combined contraceptive	3.5 (10)	5.4 (157)	0.18
Hormonal replacement therapy	4.1 (12)	2.4 (60)	0.12
Polycystic ovary syndrome	5.4 (15)	4.6 (131)	0.62
Menopausal status			
Postmenopausal	35.9 (102)	31.7 (919)	0.17
Premenopausal	64.1 (182)	68.3 (1980)	
Cigarette smoking			
Non-smoker	58.7 (166)	56.5 (1631)	0.87
Former smoker > 6 months ago	19.8 (56)	21.4 (617)	
Former smoker < 6 months ago	2.1 (6)	1.8 (53)	
Current smoker	19.4 (55)	20.2 (584)	
Alcohol use			
Non-user	11.6 (33)	11.7 (338)	0.33
Light user	79.2 (225)	81.7 (2369)	
Moderate user	3.5 (10)	3.2 (92)	
Heavy user	5.6 (16)	3.5 (102)	
Physical activity			
Inactive	19.1 (54)	21.9 (635)	0.06
Lightly active	49.1 (139)	41.0 (1185)	
Active	30.7 (87)	35.5 (1026)	
Very active	1.1 (3)	1.6 (47)	
Education			
Basic	4.4 (13)	2.0 (58)	0.01
Secondary	59.4 (174)	56.4 (1638)	
Tertiary	36.2 (106)	41.6 (1210)	
Socioeconomic status			
Entrepreneur	9.4 (26)	8.8 (246)	0.51
Higher administrative	19.1 (53)	16.7 (470)	
Lower administrative	17.0 (47)	21.0 (590)	
Blue-collar worker	47.3 (131)	47.2 (1324)	
Other	7.2 (20)	6.3 (178)	

SD = standard deviation

BMI = body mass index, calculated as weight/height squared

Menopausal status was determined by a question on climacteric symptoms on the postal questionnaire.

* P-value for Chi-Square test or Mann-Whitney U-test

Table II | Association between waist and hip circumferences and body composition, and uterine analysis.

	Unadjusted odds ratio (95% CI)	P
Waist circumference, cm	1.01 (1.00 to 1.01)	0.02
Hip circumference, cm	1.00 (1.00 to 1.01)	0.28
Waist-hip ratio	1.31 (1.13 to 1.52)	<0.001
Body composition		
Fat percentage, %	1.01 (1.00 to 1.02)	0.05
Fat mass, kg	1.01 (1.00 to 1.01)	0.24
Skeletal muscle mass, kg	1.00 (0.98 to 1.03)	0.88
Visceral fat area, cm ²	1.00 (1.00 to 1.00)	0.08
		ICD ¹
Waist circumference, cm	1.02 (1.01 to 1.03)	<0.001
Hip circumference, cm	1.01 (1.00 to 1.03)	0.008
Waist-hip ratio	1.45 (1.17 to 1.80)	0.001
Body composition		
Fat percentage, %	1.02 (1.01 to 1.04)	0.005
Fat mass, kg	1.01 (1.00 to 1.02)	0.020
Skeletal muscle mass, kg	1.01 (0.98 to 1.05)	0.51
Visceral fat area, cm ²	1.00 (1.00 to 1.01)	0.009

¹ Adjusted for parity and education.² Adjusted for parity, education, BMI and current use exogenous hormones.

Odds ratios are based on proportion of those with data on these variables.

fibroids at age 46 years, crude and adjusted odds ratio models from the logistic regression

Adjusted ¹ odds ratio (95% CI)	P	Adjusted ² odds ratio (95% CI)	P
All uterine fibroid cases (n=729)			
1.01 (1.00 to 1.01)	0.05	1.02 (1.00 to 1.04)	0.02
1.00 (1.00 to 1.01)	0.40	0.99 (0.97 to 1.01)	0.48
1.32 (1.11 to 1.58)	0.002	1.32 (1.10 to 1.57)	0.003
1.01 (1.00 to 1.02)	0.15	1.01 (0.99 to 1.04)	0.23
1.00 (1.00 to 1.01)	0.47	0.99 (0.96 to 1.02)	0.39
1.00 (0.98 to 1.03)	0.75	1.00 (0.97 to 1.03)	0.79
1.00 (1.00 to 1.00)	0.20	1.00 (1.00 to 1.01)	0.29
-code confirmed uterine fibroid cases (n=293)			
1.01 (1.00 to 1.02)	0.004	1.03 (1.01 to 1.06)	0.01
1.01 (1.00 to 1.02)	0.02	1.01 (0.98 to 1.05)	0.36
1.33 (1.04 to 1.71)	0.006	1.31 (1.02 to 1.68)	0.04
1.02 (1.00 to 1.03)	0.02	1.03 (1.00 to 1.07)	0.06
1.01 (1.00 to 1.02)	0.07	1.02 (0.98 to 1.07)	0.32
1.01 (0.98 to 1.05)	0.48	1.00 (0.95 to 1.04)	0.82
1.00 (1.00 to 1.01)	0.04	1.01 (1.00 to 1.02)	0.07

Table III | Association between glucose metabolism and uterine fibroids at age 46 years, crude and adjust

	Unadjusted odds ratio (95% CI)	P
Insulin levels in OGTT, mU/l		
Fasting	1.01 (1.00 to 1.02)	0.170
30 min*	1.02 (1.00 to 1.04)	0.12
60 min*	1.02 (1.00 to 1.03)	0.04
120 min*	1.01 (1.00 to 1.03)	0.12
Insulin AUC	1.001 (1.000 to 1.002)	0.04
Glucose levels in OGTT, mmol/l		
Fasting	1.09 (0.94 to 1.26)	0.23
30 min	1.08 (1.01 to 1.15)	0.02
60 min	1.05 (1.00 to 1.09)	0.04
120 min	1.06 (0.99 to 1.12)	0.08
Glucose AUC	1.036 (1.003 to 1.070)	0.03
OGTT indices		
Matsuda-index*	1.00 (0.98 to 1.01)	0.53
Belfiore-index**	0.97 (0.94 to 1.00)	0.04
Gutt-index*	0.97 (0.94 to 1.01)	0.10
Fasting indices		
QUICKI**	0.88 (0.66 to 1.61)	0.36
HOMA2-b*	1.01 (0.98 to 1.04)	0.68
HOMA2-IR*	1.00 (0.98 to 1.01)	0.57
Glucose tolerance status, %		
NGT <6.1 mmol/l	reference	
IFG 6.1-6.9 mmol/l	1.25 (0.76 to 1.99)	0.36
IGT ≥7.0 mmol/l	1.26 (0.90 to 1.74)	0.17
ScDM	1.12 (0.58 to 2.02)	0.73
PrevDM	1.06 (0.59 to 1.81)	0.84
Insulin levels in OGTT, mU/l		
Fasting	1.01 (0.99 to 1.02)	0.17
30 min*	1.02 (0.99 to 1.05)	0.22
60 min*	1.03 (1.00 to 1.05)	0.02
120 min*	1.02 (1.00 to 1.05)	0.07
Insulin AUC	1.002 (1.000 to 1.003)	0.02
Glucose levels in OGTT, mmol/l		
Fasting	1.11 (0.90 to 1.33)	0.29
30 min	1.15 (1.05 to 1.26)	0.003
60 min	1.06 (0.99 to 1.12)	0.08
120 min	1.08 (0.99 to 1.17)	0.08
Glucose AUC	1.053 (1.006 to 1.101)	0.03
OGTT indices		

Matsuda-index*	0.98 (0.95 to 1.00)	0.04
Belfiore-index**	0.95 (0.91 to 0.99)	0.02
Gutt-index*	0.94 (0.89 to 0.99)	0.02
Fasting indices		
QUICKI**	0.72 (0.48 to 1.09)	0.12
HOMA2-b*	1.01 (0.96 to 1.05)	0.79
HOMA2-IR*	0.99 (0.96 to 1.01)	0.38
Glucose tolerance status, %		
NGT	reference	
IFG	2.10 (1.16 to 3.58)	0.01
IGT	1.31 (0.80 to 2.05)	0.26
ScDM	0.82 (0.25 to 2.05)	0.71
PrevDM	0.79 (0.28 to 1.82)	0.63

¹ Adjusted for parity and education.

²Adjusted for parity, education, BMI and current use exogenous hormones.

Odds ratios are based on proportion of those with data on these variables.

* The odds ratios (95% CI) were calculated per 10 unit change.

** The odds ratios (95% CI) were calculated per 0.1 unit change.

The odds ratios were 1 unit unless otherwise stated.

ed odds ratio models from the logistic regression analysis.

Adjusted ¹ odds ratio (95% CI)	P	Adjusted ² odds ratio (95% CI)	P
All uterine fibroid cases			
1.00 (0.99 to 1.02)	0.580	1.00 (0.99 to 1.02)	0.71
1.02 (1.00 to 1.04)	0.07	1.02 (0.99 to 1.04)	0.18
1.02 (1.00 to 1.04)	0.03	1.01 (1.00 to 1.03)	0.11
1.01 (1.00 to 1.03)	0.13	1.01 (0.99 to 1.03)	0.41
1.001 (1.000 to 1.002)	0.14	1.001 (1.000 to 1.002)	0.21
1.04 (0.88 to 1.21)	0.62	1.04 (0.88 to 1.21)	0.65
1.05 (0.98 to 1.12)	0.15	1.05 (0.98 to 1.12)	0.17
1.03 (0.98 to 1.08)	0.27	1.02 (0.97 to 1.07)	0.39
1.04 (0.97 to 1.11)	0.28	1.03 (0.96 to 1.10)	0.38
1.022 (0.986 to 1.059)	0.22	1.018 (0.983 to 1.055)	0.32
1.00 (0.98 to 1.01)	0.51	1.00 (0.98 to 1.02)	0.92
0.97 (0.94 to 1.00)	0.05	0.98 (0.94 to 1.01)	0.19
0.97 (0.93 to 1.00)	0.08	0.98 (0.94 to 1.02)	0.26
0.88 (0.66 to 1.17)	0.38	0.96 (0.68 to 1.34)	0.80
1.01 (0.97 to 1.04)	0.72	1.00 (0.96 to 1.03)	0.84
1.00 (0.98 to 1.01)	0.59	1.00 (0.98 to 1.02)	0.91
reference		reference	
1.17 (0.70 to 1.86)	0.53	1.14 (0.69 to 1.83)	0.60
1.26 (0.90 to 1.75)	0.17	1.22 (0.86 to 1.71)	0.25
1.08 (0.55 to 1.97)	0.82	1.03 (0.52 to 1.90)	0.93
1.06 (0.58 to 1.82)	0.84	1.01 (0.54 to 1.76)	0.99
ICD-code confirmed uterine fibroid cases			
1.00 (0.99 to 1.02)	0.58	1.00 (0.99 to 1.02)	0.71
1.02 (0.99 to 1.05)	0.15	1.01 (0.98 to 1.04)	0.43
1.03 (1.01 to 1.05)	0.01	1.02 (1.00 to 1.05)	0.07
1.02 (1.00 to 1.05)	0.07	1.01 (0.99 to 1.04)	0.33
1.001 (0.999 to 1.003)	0.11	1.001 (0.999 to 1.003)	0.17
1.00 (0.78 to 1.23)	0.97	1.00 (0.78 to 1.24)	0.99
1.13 (1.03 to 1.24)	0.01	1.05 (0.98 to 1.12)	0.17
1.03 (0.98 to 1.08)	0.27	1.02 (0.97 to 1.07)	0.39
1.04 (0.97 to 1.11)	0.10	1.03 (0.96 to 1.10)	0.38
1.029 (0.978 to 1.082)	0.26	1.024 (0.972 to 1.077)	0.37

0.98 (0.95 to 1.00)	0.05	0.98 (0.96 to 1.01)	0.19
0.95 (0.91 to 0.99)	0.02	0.96 (0.91 to 1.01)	0.13
0.94 (0.88 to 0.99)	0.02	0.95 (0.89 to 1.01)	0.09
0.76 (0.50 to 1.15)	0.19	0.90 (0.55 to 1.48)	0.68
1.00 (0.96 to 1.05)	0.92	0.98 (0.93 to 1.03)	0.52
0.99 (0.96 to 1.02)	0.45	1.00 (0.97 to 1.03)	0.98
reference		reference	
1.93 (1.06 to 3.32)	0.03	1.81 (0.98 to 3.14)	0.045
1.31 (0.80 to 2.07)	0.26	1.22 (0.73 to 1.95)	0.42
0.74 (0.22 to 1.88)	0.58	0.65 (0.19 to 1.68)	0.42
0.80 (0.28 to 1.84)	0.64	0.67 (0.22 to 1.60)	0.41

Table IV | Association between serum lipids, blood pressure, metabolic syndrome, cardiovascular risk scores

	Unadjusted odds ratio (95% CI)	P
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Serum lipids, mmol/l		
Total cholesterol	1.14 (1.03 to 1.26)	0.01
HDL	0.83 (0.66 to 1.05)	0.12
LDL	1.17 (1.06 to 1.30)	0.002
Triglycerides	1.31 (1.13 to 1.51)	<0.001
Blood pressure, mmHg		
Systolic mean*	1.03 (0.98 to 1.09)	0.27
Diastolic mean*	1.02 (0.94 to 1.10)	0.70
>140/90, %	0.99 (0.78 to 1.26)	0.96
>140/90 medicated, %	1.19 (0.95 to 1.48)	0.13
Metabolic syndrome (IDF criteria), %	1.26 (1.03 to 1.52)	0.02
Cardiovascular risk scores		
Framingham CVD risk score	1.02 (0.98 to 1.05)	0.29
SCORE, %	1.29 (0.70 to 2.30)	0.40
Serum total testosterone, nmol/l	0.92 (0.73 to 1.12)	0.46
Serum SHBG, nmol/l	1.00 (1.00 to 1.00)	0.05
Fatty liver index	1.00 (0.99 to 1.01)	0.87
High sensitive CRP, mg/l		
<1, %	reference	
1-3, %	1.21 (1.00 to 1.47)	0.07
>3, %	1.02 (0.77 to 1.34)	0.88
<hr/>		
Serum lipids, mmol/l		
Total cholesterol	1.29 (1.11 to 1.49)	0.001
HDL	0.75 (0.53 to 1.05)	0.10
LDL	1.31 (1.13 to 1.51)	<0.001
Triglycerides	1.46 (1.21 to 1.76)	<0.001
Blood pressure, mmHg		
Systolic mean*	1.07 (0.99 to 1.16)	0.09
Diastolic mean*	1.08 (0.96 to 1.21)	0.20
>140/90, %	1.17 (0.83 to 1.63)	0.35
>140/90 medicated, %	1.23 (0.89 to 1.69)	0.20
Metabolic syndrome (IDF criteria), %	1.60 (1.22 to 2.08)	0.001
Cardiovascular risk scores		
Framingham CVD risk score	1.03 (0.98 to 1.07)	0.29
SCORE, %	1.83 (0.79 to 3.90)	0.14
Serum total testosterone, nmol/l	0.70 (0.47 to 1.01)	0.06
Serum SHBG, nmol/l	1.00 (0.99 to 1.00)	0.27
Fatty liver index	1.01 (1.00 to 1.02)	0.20
High sensitive CRP, mg/l		
<1, %	reference	
1-3, %	1.40 (1.05 to 1.85)	0.02

>3, %	1.02 (0.66 to 1.51)	0.94
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¹ Adjusted for parity and education.
²Adjusted for parity, education, BMI and current use exogenous hormones.
Odds ratios are based on proportion of those with data on these variables.
* The odds ratios (95% CI) were calculated per 10 mmHg change.

, serum total testosterone, serum sex hormone binding globuline (SHBG), fatty liver

Adjusted ¹ odds ratio (95% CI)	P	Adjusted ² odds ratio (95% CI)	P
All uterine fibroid cases			
1.11 (1.00 to 1.23)	0.06	1.10 (1.00 to 1.22)	0.08
0.81 (0.64 to 1.02)	0.07	0.83 (0.64 to 1.06)	0.14
1.15 (1.04 to 1.27)	0.009	1.13 (1.02 to 1.26)	0.02
1.28 (1.11 to 1.48)	0.001	1.27 (1.09 to 1.49)	0.003
1.02 (0.97 to 1.08)	0.43	1.01 (0.95 to 1.08)	0.71
1.00 (0.91 to 1.08)	0.90	0.97 (0.88 to 1.06)	0.50
0.96 (0.75 to 1.21)	0.71	0.92 (0.72 to 1.18)	0.53
1.15 (0.92 to 1.44)	0.21	1.11 (0.88 to 1.40)	0.39
1.22 (1.00 to 1.49)	0.05	1.22 (0.98 to 1.51)	0.08
1.01 (0.97 to 1.05)	0.58	1.00 (0.96 to 1.04)	0.91
1.04 (0.55 to 1.90)	0.90	0.95 (0.49 to 1.77)	0.86
0.87 (0.68 to 1.08)	0.25	0.87 (0.68 to 1.08)	0.25
1.00 (0.99 to 1.00)	0.02	1.00 (0.99 to 1.00)	0.03
1.00 (0.99 to 1.01)	0.92	0.99 (0.98 to 1.01)	0.21
reference		reference	
1.19 (0.97 to 1.46)	0.09	1.14 (0.92 to 1.41)	0.23
0.95 (0.71 to 1.26)	0.73	0.87 (0.63 to 1.19)	0.40
ICD-code confirmed uterine fibroid cases			
1.23 (1.06 to 1.43)	0.007	1.21 (1.05 to 1.41)	0.01
0.73 (0.51 to 1.02)	0.07	0.81 (0.55 to 1.16)	0.26
1.26 (1.09 to 1.46)	0.003	1.22 (1.05 to 1.42)	0.01
1.42 (1.17 to 1.72)	<0.001	1.37 (1.11 to 1.68)	0.004
1.06 (0.97 to 1.15)	0.20	1.03 (0.94 to 1.13)	0.48
1.04 (0.92 to 1.18)	0.51	1.00 (0.87 to 1.14)	0.95
1.08 (0.76 to 1.51)	0.68	1.00 (0.69 to 1.42)	1.00
1.17 (0.84 to 1.61)	0.35	1.07 (0.75 to 1.50)	0.71
1.53 (1.16 to 2.01)	0.003	1.48 (1.09 to 2.01)	0.01
1.01 (0.96 to 1.06)	0.60	0.99 (0.94 to 1.05)	0.79
1.42 (0.58 to 3.14)	0.42	1.16 (0.46 to 2.68)	0.74
0.61 (0.41 to 0.89)	0.01	0.60 (0.40 to 0.89)	0.01
1.00 (0.99 to 1.00)	0.18	1.00 (1.00 to 1.00)	0.52
1.01 (0.99 to 1.02)	0.34	0.99 (0.97 to 1.01)	0.36
reference		reference	
1.35 (1.01 to 1.80)	0.04	1.21 (0.89 to 1.65)	0.22

0.88 (0.56 to 1.33)	0.57	0.70 (0.42 to 1.12)	0.15
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Table V | Previous studies on the association between cardiovascular disease risk fac

Paper			Patients	
Body size				
Author	Year	Study design	N	Age
Samadi	1996	case-control	1,704	20 - 54
Marshall	1998	cohort	94,095	29 - 46
Sato	1998	case-control	300	29 - 54
Chen	2001	case-control	1,585	17 - 44
Faerstein	2001	case-control	712	18 - 55
Wise	2005	cohort	21,506	21 - 69
Parazzini	2006	cohort	85,967	≤51 - ≥56
Takeda	2008	case-control	372	40 - 49
Dandolu	2010	case-control	873	1 - >70
Yang	2014	case-control	826	35 - 55
Lipid metabolism				
Author	Year	Study design	N	Age
Takeda	2008	case-control	372	40 - 49
Sadlonova	2008	case-control	76	25 - 57
He	2013	case-control	661	35 - 55
Aksoy	2014	case-control	477	40 - 50
Glucose metabolism				
Author	Year	Study design	N	Age
Faerstein	2001	case-control	712	18 - 55
Templeman	2009	cohort	80,204	25 - 84
Baird	2009	case-control	988	35 - 49
He	2013	case-control	661	35 - 55
Hypertension				
Author	Year	Study design	N	Age
Parazzini	2004	case-control	2,400	21 - 54
Boynton-Jarrett	2005	cohort	104,233	35 - 52
Radin	2012	cohort	22,530	21 - 69

tors and uterine fibroids.

		Results
Fibroid diagnosis	Ancestry	Association
self-report	African-American, White and other	no association betw
self-reported ultrasound or surgery	White, African-American, Hispanic, Asian	risk of fibroids incre
surgery and histology report	Asian	risk of fibroids incre
self-report, surgery	White, African-American	no association betw
pelvic examination, ultrasound, surgery	White, African-American, other	positive associatio
self-reported ultrasound or surgery	African-American	inverse J-shaped pa
pelvic examination and clinical diagnosis, ultrasound	White	risk of fibroids incre
surgery	Asian	risk of fibroids incre
surgery	Asian, African-American, Hispanic, White	positive correlatio
ultrasound	Asian	positive associatio
Fibroid diagnosis	Ancestry	total cholesterol
surgery	Asian	
ultrasound	(not identified)	NS
surgery	Asian	NS
ultrasound, surgery	(not identified)	
Fibroid diagnosis	Ancestry	Association
pelvic examination, ultrasound, surgery	White, African-American, other	no association
hospital discharge register	White, African-American, Latin, Asian, other	inverse association
ultrasound screening	White, African-American	inverse association
surgery	Asian	no association
Fibroid diagnosis	Ancestry	Association
surgery and histology report	(not identified)	no association
self-report	White, African-American, Latin, Asian	correlation betwee
self-report	African-American	association betwee

between BMI and fibroid risk
 increased with increasing BMI
 increased with obesity
 between BMI and fibroid risk
 1 between high BMI and risk of fibroids
 pattern of association between BMI and risk of fibroids
 increased with overweight
 increased with overweight
 1 between BMI and fibroids
 1 between high BMI and risk of fibroids

HDL	LDL	triglycerides
		positive association
positive association/+	NS	NS
inverse association	NS	positive association
inverse association	NS	NS

between self-reported diabetes and fibroid risk
 with IGF-1 and insulin

with increasing blood pressure and fibroid risk
 with treated hypertension and fibroid risk
