

A Mendelian randomization study of circulating uric acid and type 2 diabetes

Running title: Mendelian randomization uric acid and diabetes

Ivonne Sluijs PhD^{(1)*}, Michael V Holmes MD, PhD^{(2,3)*}, Yvonne T van der Schouw PhD⁽¹⁾, Joline WJ Beulens PhD⁽¹⁾, Folkert W Asselbergs MD, PhD^(1,4,5), José María Huerta PhD^(6,7), Tom M Palmer PhD⁽⁸⁾, Larraitz Arriola MD, MSc^(9,10,7), Beverley Balkau PhD^(11,12), Aurelio Barricarte PhD^(13,7), Heiner Boeing PhD⁽¹⁴⁾, Françoise Clavel-Chapelon PhD^(11,12), Guy Fagherazzi PhD^(11,12), Paul W Franks PhD^(15,16), Diana Gavrilă MD MPH^(6,7), Rudolf Kaaks PhD⁽¹⁷⁾, Kay Tee Khaw MBBChir, FRCP⁽¹⁸⁾, Tilman Kühn MSc⁽¹⁷⁾, Esther Molina-Montes PhD^(19,7), Lotte Maxild Mortensen MSc^(20,21), Peter M Nilsson PhD⁽¹⁵⁾, Kim Overvad PhD^(21,22), Domenico Palli MD⁽²³⁾, Salvatore Panico MD⁽²⁴⁾, J. Ramón Quirós MD⁽²⁵⁾, Olov Rolandsson MD, PhD⁽¹⁶⁾, Carlotta Sacerdote PhD^(26,27), Núria Sala PhD⁽²⁸⁾, Julie A Schmidt MSc⁽²⁹⁾, Robert A Scott PhD⁽³⁰⁾, Sabina Sieri PhD⁽³¹⁾, Nadia Slimani PhD⁽³²⁾, Annemieke MW Spijkerman PhD⁽³³⁾, Anne Tjonneland Dr. Med. Sci⁽³⁴⁾, Ruth C Travis Dphil⁽²⁹⁾, Rosario Tumino MD, MSc, DLSHTM^(35,36), Daphne L van der A PhD⁽³³⁾, Stephen J Sharp MSc⁽³⁰⁾, Nita G Forouhi MRCP, PhD⁽³⁰⁾, Claudia Langenberg MD, PhD⁽³⁰⁾, Elio Riboli MD, MPH, ScM⁽³⁷⁾, Nicholas J Wareham MD, PhD⁽³⁰⁾, on behalf of the InterAct consortium

⁽¹⁾ University Medical Center Utrecht, Julius Center for Health Sciences and Primary Care, Utrecht, the Netherlands, ⁽²⁾ Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), Nuffield Department of Population Health, Richard Doll Building, University of Oxford, Oxford, UK, ⁽³⁾ Division of Transplantation and Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, USA ⁽⁴⁾ Department of Cardiology, Heart Long Institute, University Medical Center Utrecht, Utrecht, The Netherlands, ⁽⁵⁾ Durrer Center for Cardiogenetic Research, ICIN-Netherlands Heart Institute, Utrecht, The Netherlands, ⁽⁶⁾ Department of Epidemiology, Murcia Regional Health Council, Murcia, Spain, ⁽⁷⁾ CIBER Epidemiología y Salud Pública (CIBERESP), Spain, ⁽⁸⁾ Division of Health Sciences, Warwick

Medical School, University of Warwick, Coventry, UK, ⁽⁹⁾ Public Health Division of Gipuzkoa, San Sebastian, Spain, ⁽¹⁰⁾ Instituto BIO-Donostia, Basque Government, San Sebastian, Spain, ⁽¹¹⁾ Inserm, CESP, U1018, Villejuif, France, ⁽¹²⁾ Univ Paris-Sud, UMRS 1018, Villejuif, France, ⁽¹³⁾ Navarre Public Health Institute (ISPN), Pamplona, Spain, ⁽¹⁴⁾ German Institute of Human Nutrition Potsdam-Rehbruecke, Germany, ⁽¹⁵⁾ Lund University, Malmö, Sweden, ⁽¹⁶⁾ Umeå University, Umeå, Sweden, ⁽¹⁷⁾ German Cancer Research Center (DKFZ), Heidelberg, Germany, ⁽¹⁸⁾ University of Cambridge, Cambridge, UK, ⁽¹⁹⁾ Andalusian School of Public Health, Granada, Spain, ⁽²⁰⁾ Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark, ⁽²¹⁾ Department of Public Health, Section for Epidemiology, Aarhus University, Aarhus, Denmark, ⁽²²⁾ Aalborg University Hospital, Aalborg, Denmark, ⁽²³⁾ Cancer Research and Prevention Institute (ISPO), Florence, Italy, ⁽²⁴⁾ Dipartimento di Medicina Clinica e Chirurgia, Federico II University, Naples, Italy, ⁽²⁵⁾ Public Health Directorate, Asturias, Spain, ⁽²⁶⁾ Unit of Cancer Epidemiology, Citta' della Salute e della Scienza Hospital-University of Turin and Center for Cancer Prevention (CPO), Torino, Italy, ⁽²⁷⁾ Human Genetics Foundation (HuGeF), Torino, Italy, ⁽²⁸⁾ Unit of Nutrition, Environment and Cancer, Cancer Epidemiology Research Program, and Translational Research Laboratory, Catalan Institute of Oncology (IDIBELL), Barcelona, Spain, ⁽²⁹⁾ Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom, ⁽³⁰⁾ MRC Epidemiology Unit, University of Cambridge, Cambridge, United Kingdom, ⁽³¹⁾ Epidemiology and Prevention Unit, Milan, Italy, ⁽³²⁾ International Agency for Research on Cancer, Lyon, France, ⁽³³⁾ National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands, ⁽³⁴⁾ Danish Cancer Society Research Center, Copenhagen, Denmark, ⁽³⁵⁾ ASP Ragusa, Italy, ⁽³⁶⁾ Aire Onlus, Ragusa, Italy, ⁽³⁷⁾ School of Public Health, Imperial College London, UK

Corresponding author: Ivonne Sluijs, PhD; Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht; PO Box 85500; 3508 GA Utrecht, the Netherlands; Phone: 0031 88 7550465; Fax: 0031 88 756 8099; E-mail: i.sluijs-2@umcutrecht.nl

* contributed equally (joint first authors)

Word count: 4,000

Number of tables: 3; figures:

2 **Abstract**

3 We aimed to investigate the causal effect of circulating uric acid concentrations on type 2
4 diabetes risk. A Mendelian randomization study was performed using a genetic score with 24
5 uric acid associated loci. We used data of the EPIC-InterAct case-cohort study, comprising
6 24,265 individuals of European ancestry from eight European countries. During a mean (SD)
7 follow-up of 10 (4) years, 10,576 verified incident type 2 diabetes cases were ascertained.
8 Higher uric acid associated with higher diabetes risk following adjustment for confounders,
9 with a HR of 1.20 (95%CI: 1.11,1.30) per 59.48 $\mu\text{mol/L}$ (1 mg/dL) uric acid. The genetic
10 score raised uric acid by 17 $\mu\text{mol/L}$ (95%CI: 15,18) per SD increase, and explained 4% of
11 uric acid variation. Using the genetic score to estimate the unconfounded effect found that a
12 59.48 $\mu\text{mol/L}$ higher uric acid concentration did not have a causal effect on diabetes (HR
13 1.01, 95%CI: 0.87,1.16). Including data from DIAGRAM consortium, increasing our dataset
14 to 41,508 diabetes cases, the summary OR estimate was 0.99 (95%CI: 0.92, 1.06). In
15 conclusion, our study does not support a causal effect of circulating uric acid on diabetes risk.
16 Uric acid lowering therapies may therefore not be beneficial in reducing diabetes risk.

17

18 **Introduction**

19 Elevated serum uric acid concentrations have been associated with higher diabetes risk in
20 observational studies(1;2). Meta-analyses reported 6-17% higher diabetes risk with every
21 59.48 $\mu\text{mol/L}$ (1 mg/dL) higher uric acid concentration(1;2). If this observed association were
22 found to be causal, uric acid lowering therapies could be used in diabetes prevention.

23 However, whether uric acid causes diabetes is still a matter of debate (3;4). Uric acid
24 concentrations are closely linked to other diabetes risk factors such as obesity, which makes it
25 difficult to determine the independent effects of uric acid when limited to observational
26 analysis alone(3;4). Evidence from human intervention studies on the effect of uric acid
27 lowering therapy on glucose metabolism is very limited and inconsistent(5-7) .

28 The concept of Mendelian randomization, i.e. using genetic variants as instrumental variable,
29 can be applied to test and estimate the causal effects of risk factors on disease outcomes(8).

30 Since alleles are randomly allocated during gamete formation, the association of a genetic
31 variant with risk of a disease outcome is unlikely to be confounded by other factors. Also,
32 reverse causality is abrogated. Three meta-analyses together identified 31 loci associated with
33 uric acid(9-11). Variants at such loci can be used as genetic instruments, to estimate the
34 unconfounded effect of uric acid on diabetes risk. Only one Mendelian randomization study
35 on uric acid and diabetes risk has been previously performed(12), and reported no evidence
36 for a causal effect. That study used a small number of SNPs (8 identified in the first meta-
37 analyses(9)), and used different studies to estimate the association between the genetic score
38 and diabetes, the association between the genetic score and uric acid, and the association
39 between uric acid and diabetes (i.e. the three sides of the Mendelian randomization
40 triangle(13)).

41 In the present study, we aimed to estimate the unconfounded effect of uric acid on diabetes
42 risk, using a multi-locus Mendelian randomization approach. We performed instrumental

43 variable estimation within the same study, using data on genetic variants in 24 uric acid
44 associated loci, and measured uric acid concentrations among 24,265 individuals, including
45 10,576 incident type 2 diabetes cases. We then bolstered the sample size by including
46 summary-level data from the DIAGRAM consortium, bringing our total number of diabetes
47 cases to 41,508.

48

49 **Subjects and methods**

50

51 **Study population**

52 The EPIC-InterAct study is a large, prospective case-cohort study involving individuals from
53 eight European countries (Denmark, France, Germany, Italy, the Netherlands, Spain, Sweden,
54 and the United Kingdom [UK]; 26 study centers), which is nested within the European
55 Prospective Investigation into Cancer and Nutrition (EPIC)(14). The majority of participants
56 were aged 35 to 70 years and were recruited between 1991 and 2000, mainly from the general
57 population. The EPIC-InterAct study, drawn from a total cohort of 340,234 individuals
58 comprising 3.99 million person–years of follow-up, was designed to investigate the interplay
59 between genetic and lifestyle factors and type 2 diabetes risk(15). A total of 12,403 verified
60 incident cases of type 2 diabetes were identified. A center-stratified, random subcohort of
61 16,154 individuals was selected for analysis. Because of the random selection, this subcohort
62 also included a random set of 778 individuals who had developed incident type 2 diabetes
63 during follow-up. All participants gave written informed consent, and the study was approved
64 by the local ethics committees and the Internal Review Board of the International Agency for
65 Research on Cancer.

66 For the observational part of this analysis, we excluded participants with missing uric acid
67 (1,873) or co-variable (n=1,641) data, leaving 24,265 (10,576 cases, 14,364 subcohort
68 participants, including 675 cases in the subcohort) participants for analyses. For the
69 instrumental variable analysis, we excluded participants with missing uric acid (1,875),
70 genetic (n= 8,634; including 4,063 from Denmark, since at the time of analysis, genetic data
71 were not yet available from the Danish cohort), BMI (n=141) or biomarker (n=11) data,
72 leaving 17,118 (7,319 cases, 10,235 subcohort participants, including 436 cases in the
73 subcohort) participants for analyses.

74

75 **Diabetes**

76 Ascertainment and verification of incident diabetes has been described in detail
77 elsewhere(15). In short, incident diabetes cases were identified through self-report, linkage to
78 primary care registers, secondary care registers, medication use and hospital admissions and
79 mortality data. Information from any follow-up visit or external evidence with a date later
80 than the baseline visit was used. To increase the specificity of the case definition, we sought
81 further evidence for all cases with information on incident type 2 diabetes from <2
82 independent sources at a minimum, including individual review of medical records.
83 Participants were followed-up for occurrence of diabetes until the 31st of December 2007.

84

85 **Uric acid and other biomarkers**

86 Non-fasting blood samples were taken at baseline. Laboratory measures were carried out by
87 the Stichting Huisartsen Laboratorium Groep (Etten-Leur, the Netherlands) on serum (except
88 for participants in the Umea center (Sweden), where only plasma samples were available) or
89 erythrocyte samples that had been previously frozen at either in ultra-low temperature freezers

90 at -80°C or in liquid nitrogen. Serum uric acid, triglycerides, glucose and HDL were
91 measured using a Cobas® enzymatic assay (Roche Diagnostics, Mannheim, Germany) on a
92 Roche Hitachi Modular P analyser. Erythrocyte HbA1c was measured using Tosoh (HLC-
93 723G8) ion exchange high-performance liquid chromatography on a Tosoh G8.

94

95 **Genotyping and construction of the genetic score**

96 DNA was extracted from buffy coat from a citrated blood sample using standard procedures
97 on an automated Autopure LS DNA extraction system (Qiagen, Hilden, Germany) with
98 PUREGENE chemistry (Qiagen). In total, 8,536 (3,942 cases, 4,859 subcohort participants,
99 including 265 cases in the subcohort) participants were genotyped with a customised version of
100 the CardioMetaboChip (CardioMetaboChip+; Illumina, San Diego, CA, USA), using a
101 Sequenom iPLEX array (Sequenom, San Diego CA, USA). The remaining participants
102 ($n=8,582$; 2,941 cases, 5,812 subcohort participants, including 171 cases in the subcohort)
103 were genotyped with the Illumina 660W quad chip (Illumina, San Diego, CA, USA), using
104 TaqMan (Applied Biosystems, Carlsbad, CA, USA). Missing genotypes for participants
105 genotyped with the Illumina 660W quad chip were imputed by assigning the mean genotype
106 at each locus for cases and non-cases separately, for individuals successfully genotyped. In
107 total, genotypes for 15 out of 24 SNPs were imputed. We selected SNPs that passed the
108 significance threshold of $P < 5 \times 10^{-8}$ in three large-scale GWAS meta-analyses of uric acid(9-
109 11) that were identified from searching PubMed with key words ‘GWAS’ and ‘uric acid or
110 urate’. No SNPs were in linkage disequilibrium with each other. The alleles were coded 0, 1,
111 2, according to the number of uric acid raising alleles. We then calculated a genetic score by
112 summing the number of risk alleles. To take into account that effect sizes of individual SNPs
113 differ, we calculated a weighted genetic score, by weighing the individual SNPs by their

114 effect on uric acid, using estimates from the previously published GWAS meta-analyses(9-
115 11). **Online supplementary table 1** provides an overview of the SNPs included in the
116 genetic score, and weights assigned to each SNP.

117

118 **Co-variables**

119 Baseline information on lifestyle, diet and medical history were obtained from self-
120 administered questionnaires. Weight and height were recorded by trained health professionals
121 during a visit to a study center. Presence of hypertension was defined based on self reported
122 diagnosis and/or use of medication. Physical activity was assessed by questionnaire and
123 classified into inactive, moderately inactive, moderately active, and active, according to the
124 Cambridge Physical Activity Index(16). Glomerular filtration rate (eGFR) was estimated
125 using the Chronic Kidney Disease Epidemiology Collaboration equation, with creatinine
126 standardized to the Roche enzymatic method(17).

127

128 **Statistical analysis**

129 Associations of individual SNPs with uric acid were assessed with linear regression, among
130 the participants in the subcohort. Uric acid was modelled per 59.48 $\mu\text{mol/L}$ (1 mg/dL), SNPs
131 were modelled per uric acid increasing allele (additive model), and associations were adjusted
132 for study center. Associations of individual SNPs and the uric acid related genetic score (per
133 SD increase) with incident diabetes were examined with modified Cox regression that
134 accounted for case-cohort design (Prentice-weighted model(18)), adjusted for study center.
135 We calculated country specific HRs, and used random-effects meta-analysis to calculate a
136 pooled HR. We investigated associations of the uric acid related genetic score (per SD
137 increase) with potential confounders using linear regression for continuous and logistic
138 regression for dichotomous confounders.

139 For the observational association of uric acid and incident diabetes, we estimated country
140 specific HRs and pooled them through meta-analysis. We used I^2 to quantify heterogeneity
141 between countries. Interactions with sex, age and BMI were tested within each country by
142 including interaction terms in the multivariable models. Country-specific estimates were
143 pooled as described above.

144 For the instrumental variable estimate of uric acid on diabetes risk, we used the weighted
145 genetic score to estimate the unconfounded effect of a 59.48 $\mu\text{mol/L}$ (1 mg/dL) increase in
146 uric acid on diabetes risk. We applied the two stage control function estimator approach(19)
147 for this instrumental variable estimate. Instrumental variable estimates were adjusted for study
148 center, and in a second model sex and BMI were added. Country-specific estimates were
149 pooled as described above. The analyses were repeated in strata of sex, age, BMI, and
150 duration of follow-up . Furthermore, we generated instrumental variable estimates of uric acid
151 on glycaemic traits (non-fasting glucose and HbA1c) as described above.

152 Proportional Hazard assumptions were inspected visually using log-minus-log plots, with no
153 deviations detected.

154

155 *Sensitivity analyses*

156 Analyses were repeated after excluding participants with HbA1c >6.5% (N=22,146 for
157 observational analysis and 15,380 for instrumental variable analysis). Furthermore, the
158 observational association of uric acid and diabetes was estimated in the population used for
159 the instrumental variable analysis (N=17,118 instead of 24,265). Moreover, we re-analysed
160 the instrumental variable estimate of uric acid on diabetes risk using the non-weighted genetic
161 score, excluding SNPs that were not statistically significantly associated with uric acid in our
162 study, excluding proxy SNPs with $r^2 < 0.80$, and excluding SNPs (rs734553; rs2231142) with
163 the strongest effects on uric acid (Online supplementary table 1).

164 *Power*

165 We estimated the power for the Mendelian randomization analysis at a 2-sided alpha of 0.05
166 based on the sample size and proportion of cases, strength of the genetic instrument, and the
167 expected causal hazards ratio using the online tool mRnd
168 (<http://glimmer.rstudio.com/kn3in/mRnd/>)(20).

169

170 *Incorporation of publicly available data from **MAGIC and** **DIAGRAM** to bolster power*

171 In order to maximize power, we additionally incorporated data made publicly available by
172 GWAS consortia. For fasting glucose (n=58,074) and HOMA-IR (n=37,073), we used data
173 from the MAGIC consortium, which is a collaborative effort that combined data from
174 multiple GWAS to identify genetic determinants that impact on glycemc and metabolic traits.
175 Participants were of European ancestry, and genotyped with the MetaboChip(21). Data are
176 publicly available at: <http://www.magicinvestigators.org/>. For diabetes, we used data from
177 DIAGRAM consortium, which meta-analysed genetic variants on MetaboChip in 34,840
178 diabetes cases and 114,981 controls from 37 studies (22). All studies participating in
179 DIAGRAM included both men and women; participants were mainly of European ancestry;
180 the mean age varied from 43 to 72 years and the mean study-level BMI varied from 25.9 to
181 33.4 kg/m² among diabetes cases, and from 22.3 to 28.3 kg/m² among controls. Data are
182 publicly available at <http://diagram-consortium.org/downloads.html>.

183 For DIAGRAM, we selected the same 24 SNPs (either directly or in LD>0.85) and extracted
184 the ORs and accompanying standard errors. Diabetes estimates were meta-analysed with odds
185 ratios from InterAct (after excluding EPIC-Norfolk, which contributes to DIAGRAM) using
186 fixed-effects meta-analysis on the log scale, to generate a summary estimate for each SNP and
187 diabetes risk. We then used pooled SNP-diabetes effect estimates (including up to 41,508
188 diabetes cases) and external weights from uric acid GWAS (Online supplementary table 1) for

189 instrumental variable analysis. In MAGIC, exactly the same process was repeated but without
190 meta-analysing MAGIC and InterAct (given that fasting glucose and HOMA-IR are not
191 quantified in InterAct). We generated instrumental variable estimates for each SNP by
192 dividing each SNP-trait effect estimate by the corresponding SNP-uric acid estimate. The
193 analysis took into account the uncertainty in both the SNP-trait and SNP-uric acid estimates
194 by using the delta method to estimate standard errors of instrumental variable ratio
195 estimates(23). We then pooled instrumental variable estimates across SNPs using fixed-
196 effects meta-analysis to generate the summary causal effects.

197 All analysis were performed using Stata 13.1 (StataCorp, College Station, Texas, USA).

198

199

200 **Results**

201 The mean (SD) age in the subcohort was 52 (10) years, and 65% was men. The mean (SD)
202 uric acid concentration was 280 (77) $\mu\text{mol/L}$ among the subcohort and 333 (83) $\mu\text{mol/L}$
203 among diabetes cases (**Table 1**). Mean uric acid ranged from 327 $\mu\text{mol/L}$ in Italy and Sweden
204 to 351 $\mu\text{mol/L}$ in Spain among males, and from 241 $\mu\text{mol/L}$ in Germany to 261 $\mu\text{mol/L}$ in the
205 Netherlands among women.

206

207 **Observational association of uric acid and diabetes**

208 In the observational analysis, uric acid was associated with higher diabetes risk, with a HR of
209 1.51 (95%CI: 1.42, 1.62) per 59.48 $\mu\text{mol/L}$ (1 mg/dL) uric acid. After adjustment for
210 confounders, the observed association attenuated but remained present, with a corresponding
211 HR of 1.20 (95%CI: 1.11, 1.30) in the multivariable model. BMI was the largest contributor
212 to this attenuation (**Table 2**). Additional adjustment for red meat and vitamin C did not alter

213 the findings (HR 1.22 [95%CI: 1.11, 1.34]). The association remained consistent when we
214 explored the association using the population selected for the instrumental variable analysis
215 (HR multivariable model: 1.25 [95%CI: 1.13, 1.38]). Excluding participants with HbA1c
216 >6.5% yielded a multivariable HR of 1.26 (95%CI: 1.17, 1.36).

217 Although all country specific HRs directed towards a higher diabetes risk with higher uric
218 acid concentrations, there was substantial heterogeneity between countries (I^2 70%, P-value
219 0.001; **Online supplementary figure 1**). Heterogeneity remained present when the analyses
220 were stratified by age, sex, and BMI with no significant interactions for age and sex (P-values
221 for interaction 0.16 and 0.77, respectively) and borderline significant (P-value 0.06) for BMI
222 with no substantially different results in BMI strata; data not shown). After excluding Sweden
223 from the analysis, heterogeneity attenuated substantially, with I^2 of 48% (P-value 0.07), and
224 the association remained present (HR 1.17 [95%CI: 1.09, 1.25]).

225

226 **Associations of individual SNPs and genetic score with uric acid and diabetes**

227 Individual uric acid associated SNPs were all directly associated with uric acid, with the
228 strongest association for rs734553 on locus *SLC2A9* (Table 3). The individual SNPs were
229 generally not associated with diabetes risk (Table 3).

230 The mean (SD) uric acid associated genetic score was 1.55 (0.25) in both the subcohort and
231 diabetes cases, and normally distributed among the study participants. A one SD higher
232 genetic score associated with a 17 $\mu\text{mol/L}$ (95%CI: 15, 18) higher uric acid concentration
233 (**Online supplementary table 2**). The genetic score explained 4% of the proportion of
234 variance of uric acid (F-statistic 462). The genetic score did not associate with diabetes risk
235 (HR: 1.01 [95%CI: 0.97, 1.05] per SD higher genetic score; **Online supplementary figure**
236 **2**).

237

238 **Association of genetic score with potential confounders or mediators**

239 The uric acid associated genetic score was associated with higher triglyceride concentrations
240 (Beta: 0.01 mmol/L [95%CI: 0.001, 0.02] per SD higher genetic score) and a borderline
241 association was identified with vitamin C intake and physical activity. Remaining potential
242 confounders or mediators were not associated with the genetic score (**Online supplementary**
243 **table 3**).

244

245 **Instrumental variable analysis of uric acid and diabetes**

246 Using the uric acid associated genetic score to estimate the unconfounded effect of uric acid
247 (per 59.48 $\mu\text{mol/L}$ [1 mg/dL]) on diabetes showed no evidence for an effect (HR 1.01
248 [95%CI: 0.87, 1.16]). There was no substantial heterogeneity between countries (I^2 16%, P-
249 value 0.31; **Online supplementary figure 3**). This did not materially change after further
250 adjustment for sex and BMI (Table 2). No differential effects were found in subgroups based
251 on sex, age, BMI and duration of follow-up (**Online supplementary table 4**). Furthermore,
252 there was no evidence for an effect of uric acid on glycemetic traits (**Online supplementary**
253 **table 5**).

254 Excluding participants with HbA1c >6.5% yielded a HR of 1.02 (95%CI: 0.89, 1.17). Using
255 the non-weighted genetic score as the instrumental variable instead of the weighted genetic
256 score yielded a HR of 0.96 (95%CI: 0.71, 1.30). Excluding SNPs from the weighted genetic
257 score that were not associated with uric acid in our study did not change our findings (HR
258 1.02 [95%CI: 0.89, 1.17]), and neither did excluding proxy SNPs with $r^2 < 0.80$ (HR 0.99

259 (0.85, 1.16). Adjustment for triglycerides, vitamin C and physical activity did not materially
260 alter the estimate (HR 0.97 [95% CI: 0.82, 1.15]).

261 Inclusion of DIAGRAM, increasing our dataset to 41,508 diabetes cases yielded a summary
262 causal estimate of OR 0.99 (95% CI: 0.92, 1.06) (Table 2; **Online supplementary figure 4**).
263 Using this combined dataset, exclusion of the two SNPs that most strongly associated with
264 circulating uric acid (rs734553 in *SLC2A9* and/or rs2231142 in *ABCG2*) did not alter the
265 summary estimate (**Online supplementary table 6**).

266

267 **Power calculation**

268 Power calculations for our Mendelian randomization analysis are shown in **Online**
269 **supplementary table 7**. In InterAct, we had 100% power to detect a HR of 1.51, 68% power
270 to detect a HR of 1.20, and 31% power to detect the same effect estimate when we excluded
271 rs734553. Inclusion of DIAGRAM increased power to detect a HR of 1.2 for all sensitivity
272 analyses to over 90% (**Online supplementary Table 7**), meaning that the estimates derived
273 from the combined analysis (InterAct and DIAGRAM) were well powered for all scenarios.

274

275 **Discussion**

276 In this large European case-cohort study, we found a 20% higher diabetes risk per 59.48
277 $\mu\text{mol/L}$ (1 mg/dL) higher circulating uric acid concentration in multivariable observational
278 analysis. Instrumental variable analysis did not confirm this association, and suggests no
279 evidence of a causal effect of circulating uric acid on diabetes risk.

280 The results of the observational analysis are in line with previous reports(1;2). Two previous
281 meta-analyses showed 6-17% higher diabetes risk per 59.48 $\mu\text{mol/L}$ (1 mg/dL) uric acid. We
282 found a 20% higher risk per 59.48 $\mu\text{mol/L}$ (1 mg/dL) which is comparable to the previous
283 studies. However, residual confounding and/or reverse causality may explain these
284 associations, since we did not find evidence for such an association in instrumental variable
285 analysis. The results of our instrumental variable analysis generally agree with previous
286 studies. First of all, our findings are in agreement with the previously performed Mendelian
287 randomization study of uric acid and diabetes, that included fewer uric acid associated loci
288 and used different studies to estimate the three sides of the Mendelian randomization
289 triangle(12). Moreover, a study of Yang et al.(11) showed no association of a genetic score
290 for uric acid with plasma glucose concentrations, in line with our results. Studies that used a
291 genetic uric acid score or *SLC2A9* as instrumental variable also suggested a bystander role for
292 uric acid in other metabolic and cardiovascular traits, namely metabolic syndrome(24;25),
293 ischemic heart disease(26), markers of subclinical atherosclerosis(27), markers of
294 adiposity(28), and triglycerides(29). For blood pressure, the results are mixed, with reports of
295 no effect(26), reducing effects(30;31), and increasing effects(32) (**Online supplementary**
296 **Table 8**).

297 There are observations that support a potential causal role of uric acid, whereas others suggest
298 a bystander role. First of all, hyperinsulinemia decreases renal excretion of uric acid, leading
299 to increased blood concentrations of uric acid(3), supporting a bystander role. Furthermore,
300 sub-clinical chronic inflammation may precede the development of diabetes(33), and uric acid
301 generation may be increased as a result of oxidative stress. Support for a causal role comes
302 from a recent study showing that intestinal knockdown of uric acid resulted in hyperuricemia
303 and development of metabolic syndrome in mice(34). Moreover, there are reports that
304 xanthine oxidase inhibitors (pharmacological agents used to lower uric acid) may improve

305 endothelial function, what may reduce insulin resistance(3). However, it has been suggested
306 that this may represent an additional effect of enzyme inhibition that is unrelated to uric acid,
307 since therapies other than xanthine oxidase inhibitors that reduce uric acid concentrations did
308 not show the same benefits to endothelial function(7;35). Inhibition of xanthine oxidase may
309 improve endothelial function by reduction of oxidative stress instead of lowering of uric acid
310 (7).

311 Strengths of our study are its large sample size (especially including data from DIAGRAM,
312 which provided a cumulative total of over 40,000 diabetes cases and bolstered our power for
313 sensitivity analyses), heterogeneous European population, and availability of a comprehensive
314 range of potential confounders. Moreover, uric acid concentrations were available for all
315 participants, and were measured centrally to optimize comparability of uric acid
316 concentrations among participants. Furthermore, our findings showed robustness in sensitivity
317 analysis. A potential limitation of our study includes that the genetic score explained only 4%
318 of variation in uric acid. The percentage of explained variation is very comparable to previous
319 Mendelian randomization studies(36), and the corresponding F-statistic was high, indicating
320 we are unlikely to suffer from weak instrument bias(13). Second, our study investigated the
321 effect of circulating uric acid in blood, and does not necessarily also reflect effects of
322 intracellular uric acid. Individual SNPs in the gene score may have differential effects on uric
323 acid concentration by body compartment(34;37). Despite this, it is not plausible there will be
324 common pleiotropy among the individual SNPs included in the score, and any pleiotropic
325 roles of SNPs should be balanced out by use of a polygenic score(38). Third, our study
326 population was of European ancestry, which limits generalizability to populations of other
327 ancestries.

328 Mendelian randomization studies are a valid way to explore evidence for causality, given that
329 certain assumptions are met. First, there has to be a strong association between the

330 instrumental variable and risk factor of interest. All SNPs used in this study have previously
331 been shown to be strongly associated with uric acid concentrations in large meta-analyses of
332 genome wide association studies(9-11). Nevertheless, some SNPs did not associate with uric
333 acid in our study. However, when we excluded those SNPs from the genetic score, the null-
334 association remained present. Moreover, we strengthened our instrumental variable by using a
335 genetic score of multiple uric acid associated SNPs. No SNPs were in linkage disequilibrium
336 with each other, which justifies combining those SNPs.

337 Second, the instrumental variable must be independent of potential confounders (confounders
338 in the association between uric acid and diabetes). To test this, we examined the associations
339 of the genetic score with potential confounders, and found an association with triglycerides.
340 However, it can be debated whether this is a true confounder, or downstream consequence of
341 uric acid pathways. Moreover, since we did not find an association of uric acid and diabetes in
342 instrumental variable analysis, it is not likely that this is explained by the higher risk of
343 hypertriglyceridemia in individuals with a high genetic score. Indeed, when we additionally
344 adjusted the instrumental variable estimate of uric acid on diabetes risk for triglycerides, the
345 null-effect remained. The observed higher triglyceride concentrations suggests that, although
346 uric acid may not be causally involved in development of diabetes, there may be a separate
347 causal role for uric acid in this metabolic disorder.

348 Third, the instrumental variable affects the outcome only through the risk factor of interest.
349 This assumption is untestable, and should be considered using information on the underlying
350 biology. None of the SNPs used in this study were in linkage disequilibrium with loci known
351 to influence diabetes risk(22;39;40), which strengthens this assumption. Moreover, the vast
352 majority of SNPs identified in the meta-analysis of Kolz et al.(9) were involved in regulating
353 urate transport across cell membranes, which suggests that these SNPs directly influence uric
354 acid levels. However, *SLC2A9*, the strongest uric acid associated locus, does not only

355 transport uric acid, but also glucose and fructose(41), and exchanges uric acid for glucose(42),
356 leaving room for possible pleiotropy. Moreover, *SLC2A9* has recently been shown to have
357 differential effects on urinary and intestinal secretion of uric acid in mouse, suggesting a rise
358 serum uric acid due to reduced urinary secretion could be counterbalanced by increased
359 intestinal secretion and decreased portal vein levels(34). Similar contrasting roles have been
360 reported for *ABCG2*(37). A sensitivity analysis excluding the SNPs in these loci did not alter
361 the result (Online supplementary table 6).

362 In conclusion, our study does not support the hypothesis that circulating uric acid has a causal
363 effect on diabetes risk. Our findings therefore suggest that increased uric acid concentrations
364 are a consequence of an adverse metabolic profile, rather than a cause of diabetes, and that
365 uric acid has limited value as therapeutic target in preventing diabetes.

Acknowledgements

We thank staff from the Technical, Field Epidemiology and Data Functional Group Teams of the MRC Epidemiology Unit in Cambridge, UK, for carrying out sample preparation, DNA provision and quality control, genotyping and data-handling work. We specifically thank S. Dawson for coordinating the sample provision for biomarker measurements, A. Britten for coordinating DNA sample provision and genotyping of candidate markers, N. Kerrison, C. Gillson and A. Britten for data provision and genotyping quality control and M. Sims for writing the technical laboratory specification for the intermediate pathway biomarker measurements and for overseeing the laboratory work (all MRC Epidemiology Unit, Cambridge, UK). We thank all EPIC participants and staff for their contribution to the study. We thank N. Kerrison (MRC Epidemiology Unit, Cambridge, UK) for managing the data for the EPIC-InterAct Project.

Funding for the EPIC-InterAct project was provided by the EU FP6 programme (grant number LSHM_CT_2006_037197). In addition, EPIC-InterAct investigators acknowledge funding from the following agencies: I.S., Y.T.S., J.W.J.B.: Verification of diabetes cases was additionally funded by NL Agency grant IGE05012 and an Incentive Grant from the Board of the UMC Utrecht; M.V.H.: MRC Population Health Scientist Fellowship (G0802432); J.M.H.: Health Research Fund of the Spanish Ministry of Health; Murcia Regional Government (N° 6236); P.W.F., P.M.N.: Swedish Research Council; P.W.F.: Novo Nordisk, Swedish Diabetes Association, Swedish Heart-Lung Foundation; R.K.: German Cancer Aid, German Ministry of Research (BMBF); K.T.K.: Medical Research Council UK, Cancer Research UK; T.K.: German Cancer Aid, German Cancer Research Center (DKFZ), German Federal Ministry of Education and Research (BMBF); K.O., A.T.: Danish Cancer Society; S.P.: Compagnia di San Paolo; J.R.Q.: Asturias Regional Government; O.R.: The Västerboten

County Council; N.S.: Spanish Ministry of Health network RTICCC (ISCIII RD06/0020/0091)); A.M.W.S.,D.L. A.: Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), Statistics Netherlands; R.T.: AIRE-ONLUS Ragusa, AVIS-Ragusa, Sicilian Regional Government.

Author contributions were as follows: I.S. had access to all data for this study, analysed the data, drafted the manuscript, and takes responsibility for the manuscript contents. M.V.H. helped with analyses and drafting of the manuscript. Analytical tools were provided by T.P. All authors qualify for authorship according to Diabetes criteria. They have all contributed to conception and design, and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published. I.S. is the guarantor.

None of the authors declares a conflict of interest.

Reference List

1. Kodama,S, Saito,K, Yachi,Y, Asumi,M, Sugawara,A, Totsuka,K, Saito,A, Sone,H: Association between serum uric acid and development of type 2 diabetes. *Diabetes Care* 32:1737-1742, 2009
2. Lv,Q, Meng,XF, He,FF, Chen,S, Su,H, Xiong,J, Gao,P, Tian,XJ, Liu,JS, Zhu,ZH, Huang,K, Zhang,C: High serum uric acid and increased risk of type 2 diabetes: a systemic review and meta-analysis of prospective cohort studies. *PLoS One* 8:e56864, 2013
3. Feig,DI, Kang,DH, Johnson,RJ: Uric acid and cardiovascular risk. *N Engl J Med* 359:1811-1821, 2008
4. Tsouli,SG, Liberopoulos,EN, Mikhailidis,DP, Athyros,VG, Elisaf,MS: Elevated serum uric acid levels in metabolic syndrome: an active component or an innocent bystander? *Metabolism* 55:1293-1301, 2006
5. Ogino,K, Kato,M, Furuse,Y, Kinugasa,Y, Ishida,K, Osaki,S, Kinugawa,T, Igawa,O, Hisatome,I, Shigemasa,C, Anker,SD, Doehner,W: Uric acid-lowering treatment with benzbromarone in patients with heart failure: a double-blind placebo-controlled crossover preliminary study. *Circ Heart Fail* 3:73-81, 2010
6. Perez-Pozo,SE, Schold,J, Nakagawa,T, Sanchez-Lozada,LG, Johnson,RJ, Lillo,JL: Excessive fructose intake induces the features of metabolic syndrome in healthy adult men: role of uric acid in the hypertensive response. *Int J Obes (Lond)* 34:454-461, 2010
7. George,J, Carr,E, Davies,J, Belch,JJ, Struthers,A: High-dose allopurinol improves endothelial function by profoundly reducing vascular oxidative stress and not by lowering uric acid. *Circulation* 114:2508-2516, 2006
8. Davey Smith,G, Ebrahim,S: Mendelian randomization: prospects, potentials, and limitations. *Int J Epidemiol* 33:30-42, 2004
9. Kolz,M, Johnson,T, Sanna,S, Teumer,A, Vitart,V, Perola,M, Mangino,M, Albrecht,E, Wallace,C, Farrall,M, Johansson,A, Nyholt,DR, Aulchenko,Y, Beckmann,JS, Bergmann,S, Bochud,M, Brown,M, Campbell,H, Connell,J, Dominiczak,A, Homuth,G, Lamina,C, McCarthy,MI, Meitinger,T, Mooser,V, Munroe,P, Nauck,M, Peden,J, Prokisch,H, Salo,P, Salomaa,V, Samani,NJ, Schlessinger,D, Uda,M, Volker,U, Waeber,G, Waterworth,D, Wang-Sattler,R, Wright,AF, Adamski,J, Whitfield,JB, Gyllensten,U, Wilson,JF, Rudan,I, Pramstaller,P, Watkins,H, Doering,A, Wichmann,HE, Spector,TD, Peltonen,L, Volzke,H, Nagaraja,R, Vollenweider,P, Caulfield,M, Illig,T, Gieger,C: Meta-analysis of 28,141 individuals identifies common variants within five new loci that influence uric acid concentrations. *PLoS Genet* 5:e1000504, 2009
10. Kottgen,A, Albrecht,E, Teumer,A, Vitart,V, Krumsiek,J, Hundertmark,C, Pistis,G, Ruggiero,D, O'Seaghdha,CM, Haller,T, Yang,Q, Tanaka,T, Johnson,AD, Kutalik,Z, Smith,AV, Shi,J, Struchalin,M, Middelberg,RP, Brown,MJ, Gaffo,AL, Pirastu,N, Li,G, Hayward,C, Zemunik,T, Huffman,J, Yengo,L, Zhao,JH, Demirkan,A, Feitosa,MF, Liu,X, Malerba,G, Lopez,LM, van der,HP, Li,X, Kleber,ME, Hicks,AA, Nolte,IM, Johansson,A, Murgia,F, Wild,SH, Bakker,SJ, Peden,JF, Dehghan,A, Steri,M, Tenesa,A, Lagou,V, Salo,P, Mangino,M, Rose,LM, Lehtimaki,T, Woodward,OM, Okada,Y, Tin,A, Muller,C, Oldmeadow,C, Putku,M, Czamara,D, Kraft,P, Froggeri,L, Thun,GA, Grotevendt,A, Gislason,GK, Harris,TB, Launer,LJ, McArdle,P, Shuldiner,AR, Boerwinkle,E, Coresh,J, Schmidt,H, Schallert,M, Martin,NG, Montgomery,GW, Kubo,M, Nakamura,Y, Tanaka,T, Munroe,PB, Samani,NJ, Jacobs,DR, Jr., Liu,K, D'Adamo,P, Ulivi,S, Rotter,JI, Psaty,BM, Vollenweider,P, Waeber,G, Campbell,S, Devuyst,O, Navarro,P, Kolcic,I, Hastie,N, Balkau,B, Froguel,P, Esko,T, Salumets,A, Khaw,KT, Langenberg,C, Wareham,NJ, Isaacs,A, Kraja,A, Zhang,Q, Wild,PS, Scott,RJ, Holliday,EG, Org,E, Viigimaa,M, Bandinelli,S, Metter,JE, Lupo,A, Trabetti,E, Sorice,R, Doring,A, Lattka,E, Strauch,K, Theis,F, Waldenberger,M, Wichmann,HE, Davies,G, Gow,AJ, Bruinenberg,M, Stolk,RP, Kooner,JS, Zhang,W, Winkelmann,BR, Boehm,BO, Lucae,S, Penninx,BW, Smit,JH, Curhan,G, Mudgal,P, Plenge,RM, Portas,L, Persico,I, Kirin,M, Wilson,JF, Mateo,L, I, van Gilst,WH, Goel,A, Ongen,H, Hofman,A, Rivadeneira,F, Uitterlinden,AG, Imboden,M, von,EA, Cucca,F,

- Nagaraja,R, Piras,MG, Nauck,M, Schurmann,C, Budde,K, Ernst,F, Farrington,SM, Theodoratou,E, Prokopenko,I, Stumvoll,M, Jula,A, Perola,M, Salomaa,V, Shin,SY, Spector,TD, Sala,C, Ridker,PM, Kahonen,M, Viikari,J, Hengstenberg,C, Nelson,CP, Meschia,JF, Nalls,MA, Sharma,P, Singleton,AB, Kamatani,N, Zeller,T, Burnier,M, Attia,J, Laan,M, Klopp,N, Hillege,HL, Kloiber,S, Choi,H, Pirastu,M, Tore,S, Probst-Hensch,NM, Volzke,H, Gudnason,V, Parsa,A, Schmidt,R, Whitfield,JB, Fornage,M, Gasparini,P, Siscovick,DS, Polasek,O, Campbell,H, Rudan,I, Bouatia-Naji,N, Metspalu,A, Loos,RJ, van Duijn,CM, Borecki,IB, Ferrucci,L, Gambaro,G, Deary,IJ, Wolfenbittel,BH, Chambers,JC, Marz,W, Pramstaller,PP, Snieder,H, Gyllenstein,U, Wright,AF, Navis,G, Watkins,H, Witteman,JC, Sanna,S, Schipf,S, Dunlop,MG, Tonjes,A, Ripatti,S, Soranzo,N, Toniolo,D, Chasman,DI, Raitakari,O, Kao,WH, Ciullo,M, Fox,CS, Caulfield,M, Bochud,M, Gieger,C: Genome-wide association analyses identify 18 new loci associated with serum urate concentrations. *Nat Genet* 45:145-154, 2013
11. Yang,Q, Kottgen,A, Dehghan,A, Smith,AV, Glazer,NL, Chen,MH, Chasman,DI, Aspelund,T, Eiriksdottir,G, Harris,TB, Launer,L, Nalls,M, Hernandez,D, Arking,DE, Boerwinkle,E, Grove,ML, Li,M, Linda Kao,WH, Chonchol,M, Haritunians,T, Li,G, Lumley,T, Psaty,BM, Shlipak,M, Hwang,SJ, Larson,MG, O'Donnell,CJ, Upadhyay,A, van Duijn,CM, Hofman,A, Rivadeneira,F, Stricker,B, Uitterlinden,AG, Pare,G, Parker,AN, Ridker,PM, Siscovick,DS, Gudnason,V, Witteman,JC, Fox,CS, Coresh,J: Multiple genetic loci influence serum urate levels and their relationship with gout and cardiovascular disease risk factors. *Circ Cardiovasc Genet* 3:523-530, 2010
 12. Pfister,R, Barnes,D, Luben,R, Forouhi,NG, Bochud,M, Khaw,KT, Wareham,NJ, Langenberg,C: No evidence for a causal link between uric acid and type 2 diabetes: a Mendelian randomisation approach. *Diabetologia* 54:2561-2569, 2011
 13. Lawlor,DA, Harbord,RM, Sterne,JA, Timpson,N, Davey Smith,G: Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. *Stat Med* 27:1133-1163, 2008
 14. Riboli,E, Kaaks,R: The EPIC Project: rationale and study design. European Prospective Investigation into Cancer and Nutrition. *Int J Epidemiol* 26 Suppl 1:S6-14, 1997
 15. Langenberg,C, Sharp,S, Forouhi,NG, Franks,PW, Schulze,MB, Kerrison,N, Ekelund,U, Barroso,I, Panico,S, Tormo,MJ, Spranger,J, Griffin,S, van der Schouw,YT, Amiano,P, Ardanaz,E, Arriola,L, Balkau,B, Barricarte,A, Beulens,JW, Boeing,H, Bueno-De-Mesquita,HB, Buijsse,B, Chirlaque,L, Clavel-Chapelon,F, Crowe,FL, de Lauzon-Guillan,B, Deloukas,P, Dorronsoro,M, Drogan,D, Froguel,P, Gonzalez,C, Grioni,S, Groop,L, Groves,C, Hainaut,P, Halkjaer,J, Hallmans,G, Hansen,T, Huerta Castano,JM, Kaaks,R, Key,TJ, Khaw,KT, Koulman,A, Mattiello,A, Navarro,C, Nilsson,P, Norat,T, Overvad,K, Palla,L, Palli,D, Pedersen,O, Peeters,PH, Quiros,JR, Ramachandran,A, Rodriguez-Suarez,L, Rolandsson,O, Romaguera,D, Romieu,I, Sacerdote,C, Sanchez,MJ, Sandbaek,A, Slimani,N, Sluijs,I, Spijkerman,AM, Teucher,B, Tjonneland,A, Tumino,R, van der,AD, Verschuren,WM, Tuomilehto,J, Feskens,E, McCarthy,M, Riboli,E, Wareham,NJ: Design and cohort description of the InterAct Project: an examination of the interaction of genetic and lifestyle factors on the incidence of type 2 diabetes in the EPIC Study. *Diabetologia* 54:2272-2282, 2011
 16. Wareham,NJ, Jakes,RW, Rennie,KL, Schuit,J, Mitchell,J, Hennings,S, Day,NE: Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Public Health Nutr* 6:407-413, 2003
 17. Levey,AS, Stevens,LA, Schmid,CH, Zhang,YL, Castro,AF, III, Feldman,HI, Kusek,JW, Eggers,P, Van,LF, Greene,T, Coresh,J: A new equation to estimate glomerular filtration rate. *Ann Intern Med* 150:604-612, 2009
 18. Prentice,RL: A Case-Cohort Design for Epidemiologic Cohort Studies and Disease Prevention Trials. *Biometrika* 73:1-11, 1986
 19. Palmer,TM, Sterne,JA, Harbord,RM, Lawlor,DA, Sheehan,NA, Meng,S, Granell,R, Davey Smith,G, Didelez,V: Instrumental variable estimation of causal risk ratios and causal odds ratios in Mendelian randomization analyses. *Am J Epidemiol* 173:1392-1403, 2011
 20. Brion,MJ, Shakhbazov,K, Visscher,PM: Calculating statistical power in Mendelian randomization studies. *Int J Epidemiol* 42:1497-1501, 2013

21. Scott,RA, Lagou,V, Welch,RP, Wheeler,E, Montasser,ME, Luan,J, Magi,R, Strawbridge,RJ, Rehnberg,E, Gustafsson,S, Kanoni,S, Rasmussen-Torvik,LJ, Yengo,L, Lecoeur,C, Shungin,D, Sanna,S, Sidore,C, Johnson,PC, Jukema,JW, Johnson,T, Mahajan,A, Verweij,N, Thorleifsson,G, Hottenga,JJ, Shah,S, Smith,AV, Sennblad,B, Gieger,C, Salo,P, Perola,M, Timpson,NJ, Evans,DM, Pourcain,BS, Wu,Y, Andrews,JS, Hui,J, Bielak,LF, Zhao,W, Horikoshi,M, Navarro,P, Isaacs,A, O'Connell,JR, Stirrups,K, Vitart,V, Hayward,C, Esko,T, Mihailov,E, Fraser,RM, Fall,T, Voight,BF, Raychaudhuri,S, Chen,H, Lindgren,CM, Morris,AP, Rayner,NW, Robertson,N, Rybin,D, Liu,CT, Beckmann,JS, Willems,SM, Chines,PS, Jackson,AU, Kang,HM, Stringham,HM, Song,K, Tanaka,T, Peden,JF, Goel,A, Hicks,AA, An,P, Muller-Nurasyid,M, Franco-Cereceda,A, Folkersen,L, Marullo,L, Jansen,H, Oldehinkel,AJ, Bruinenberg,M, Pankow,JS, North,KE, Forouhi,NG, Loos,RJ, Edkins,S, Varga,TV, Hallmans,G, Oksa,H, Antonella,M, Nagaraja,R, Trompet,S, Ford,I, Bakker,SJ, Kong,A, Kumari,M, Gigante,B, Herder,C, Munroe,PB, Caulfield,M, Antti,J, Mangino,M, Small,K, Miljkovic,I, Liu,Y, Atalay,M, Kiess,W, James,AL, Rivadeneira,F, Uitterlinden,AG, Palmer,CN, Doney,AS, Willemsen,G, Smit,JH, Campbell,S, Polasek,O, Bonnycastle,LL, Herberg,S, Dimitriou,M, Bolton,JL, Fowkes,GR, Kovacs,P, Lindstrom,J, Zemunik,T, Bandinelli,S, Wild,SH, Basart,HV, Rathmann,W, Grallert,H, Maerz,W, Kleber,ME, Boehm,BO, Peters,A, Pramstaller,PP, Province,MA, Borecki,IB, Hastie,ND, Rudan,I, Campbell,H, Watkins,H, Farrall,M, Stumvoll,M, Ferrucci,L, Waterworth,DM, Bergman,RN, Collins,FS, Tuomilehto,J, Watanabe,RM, de Geus,EJ, Penninx,BW, Hofman,A, Oostra,BA, Psaty,BM, Vollenweider,P, Wilson,JF, Wright,AF, Hovingh,GK, Metspalu,A, Uusitupa,M, Magnusson,PK, Kyvik,KO, Kaprio,J, Price,JF, Dedoussis,GV, Deloukas,P, Meneton,P, Lind,L, Boehnke,M, Shuldiner,AR, van Duijn,CM, Morris,AD, Toenjes,A, Peyser,PA, Beilby,JP, Korner,A, Kuusisto,J, Laakso,M, Bornstein,SR, Schwarz,PE, Lakka,TA, Rauramaa,R, Adair,LS, Davey Smith,G, Spector,TD, Illig,T, de, FU, Hamsten,A, Gudnason,V, Kivimaki,M, Hingorani,A, Keinanen-Kiukaanniemi,SM, Saaristo,TE, Boomsma,DI, Stefansson,K, van der Harst,P, Dupuis,J, Pedersen,NL, Sattar,N, Harris,TB, Cucca,F, Ripatti,S, Salomaa,V, Mohlke,KL, Balkau,B, Froguel,P, Pouta,A, Jarvelin,MR, Wareham,NJ, Bouatia-Naji,N, McCarthy,MI, Franks,PW, Meigs,JB, Teslovich,TM, Florez,JC, Langenberg,C, Ingelsson,E, Prokopenko,I, Barroso,I: Large-scale association analyses identify new loci influencing glycemic traits and provide insight into the underlying biological pathways. *Nat Genet* 44:991-1005, 2012
22. Morris,AP, Voight,BF, Teslovich,TM, Ferreira,T, Segre,AV, Steinthorsdottir,V, Strawbridge,RJ, Khan,H, Grallert,H, Mahajan,A, Prokopenko,I, Kang,HM, Dina,C, Esko,T, Fraser,RM, Kanoni,S, Kumar,A, Lagou,V, Langenberg,C, Luan,J, Lindgren,CM, Muller-Nurasyid,M, Pechlivanis,S, Rayner,NW, Scott,LJ, Wiltshire,S, Yengo,L, Kinnunen,L, Rossin,EJ, Raychaudhuri,S, Johnson,AD, Dimas,AS, Loos,RJ, Vedantam,S, Chen,H, Florez,JC, Fox,C, Liu,CT, Rybin,D, Couper,DJ, Kao,WH, Li,M, Cornelis,MC, Kraft,P, Sun,Q, van Dam,RM, Stringham,HM, Chines,PS, Fischer,K, Fontanillas,P, Holmen,OL, Hunt,SE, Jackson,AU, Kong,A, Lawrence,R, Meyer,J, Perry,JR, Platou,CG, Potter,S, Rehnberg,E, Robertson,N, Sivapalaratnam,S, Stancakova,A, Stirrups,K, Thorleifsson,G, Tikkanen,E, Wood,AR, Almgren,P, Atalay,M, Benediktsson,R, Bonnycastle,LL, Burt,N, Carey,J, Charpentier,G, Crenshaw,AT, Doney,AS, Dorkhan,M, Edkins,S, Emilsson,V, Eury,E, Forsen,T, Gertow,K, Gigante,B, Grant,GB, Groves,CJ, Guiducci,C, Herder,C, Hreidarsson,AB, Hui,J, James,A, Jonsson,A, Rathmann,W, Klopp,N, Kravic,J, Krjutskov,K, Langford,C, Leander,K, Lindholm,E, Lobbens,S, Mannisto,S, Mirza,G, Muhleisen,TW, Musk,B, Parkin,M, Rallidis,L, Saramies,J, Sennblad,B, Shah,S, Sigurethsson,G, Silveira,A, Steinbach,G, Thorand,B, Trakalo,J, Veglia,F, Wennauer,R, Winckler,W, Zabaneh,D, Campbell,H, van,DC, Uitterlinden,AG, Hofman,A, Sijbrands,E, Abecasis,GR, Owen,KR, Zeggini,E, Trip,MD, Forouhi,NG, Syvanen,AC, Eriksson,JG, Peltonen,L, Nothen,MM, Balkau,B, Palmer,CN, Lyssenko,V, Tuomi,T, Isomaa,B, Hunter,DJ, Qi,L, Shuldiner,AR, Roden,M, Barroso,I, Wilsgaard,T, Beilby,J, Hovingh,K, Price,JF, Wilson,JF, Rauramaa,R, Lakka,TA, Lind,L, Dedoussis,G, Njolstad,I, Pedersen,NL, Khaw,KT, Wareham,NJ, Keinanen-Kiukaanniemi,SM, Saaristo,TE, Korpi-Hyovalti,E, Saltevo,J, Laakso,M, Kuusisto,J, Metspalu,A, Collins,FS, Mohlke,KL, Bergman,RN, Tuomilehto,J, Boehm,BO, Gieger,C, Hveem,K, Cauchi,S, Froguel,P, Baldassarre,D, Tremoli,E, Humphries,SE, Saleheen,D, Danesh,J, Ingelsson,E, Ripatti,S,

- Salomaa,V, Erbel,R, Jockel,KH, Moebus,S, Peters,A, Illig,T, de,FU, Hamsten,A, Morris,AD, Donnelly,PJ, Frayling,TM, Hattersley,AT, Boerwinkle,E, Melander,O, Kathiresan,S, Nilsson,PM, Deloukas,P, Thorsteinsdottir,U, Groop,LC, Stefansson,K, Hu,F, Pankow,JS, Dupuis,J, Meigs,JB, Altshuler,D, Boehnke,M, McCarthy,MI: Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. *Nat Genet* 44:981-990, 2012
23. Thomas,DC, Lawlor,DA, Thompson,JR: Re: Estimation of bias in nongenetic observational studies using "Mendelian triangulation" by Bautista et al. *Ann Epidemiol* 17:511-513, 2007
 24. McKeigue,PM, Campbell,H, Wild,S, Vitart,V, Hayward,C, Rudan,I, Wright,AF, Wilson,JF: Bayesian methods for instrumental variable analysis with genetic instruments ('Mendelian randomization'): example with urate transporter SLC2A9 as an instrumental variable for effect of urate levels on metabolic syndrome. *Int J Epidemiol* 39:907-918, 2010
 25. Dai,X, Yuan,J, Yao,P, Yang,B, Gui,L, Zhang,X, Guo,H, Wang,Y, Chen,W, Wei,S, Miao,X, Li,X, Min,X, Yang,H, Fang,W, Liang,Y, Hu,FB, Wu,T, He,M: Association between serum uric acid and the metabolic syndrome among a middle- and old-age Chinese population. *Eur J Epidemiol* 28:669-676, 2013
 26. Palmer,TM, Nordestgaard,BG, Benn,M, Tybjaerg-Hansen,A, Davey Smith,G, Lawlor,DA, Timpson,NJ: Association of plasma uric acid with ischaemic heart disease and blood pressure: mendelian randomisation analysis of two large cohorts. *BMJ* 347:f4262, 2013
 27. Oikonen,M, Wendelin-Saarenhovi,M, Lyytikainen,LP, Siitonen,N, Loo,BM, Jula,A, Seppala,I, Saarikoski,L, Lehtimaki,T, Hutri-Kahonen,N, Juonala,M, Kahonen,M, Huupponen,R, Viikari,JS, Raitakari,OT: Associations between serum uric acid and markers of subclinical atherosclerosis in young adults. The cardiovascular risk in Young Finns study. *Atherosclerosis* 223:497-503, 2012
 28. Lyngdoh,T, Vuistiner,P, Marques-Vidal,P, Rousson,V, Waeber,G, Vollenweider,P, Bochud,M: Serum uric acid and adiposity: deciphering causality using a bidirectional Mendelian randomization approach. *PLoS One* 7:e39321, 2012
 29. Rasheed,H, Hughes,K, Flynn,TJ, Merriman,TR: Mendelian Randomization Provides No Evidence for a Causal Role of Serum Urate in Increasing Serum Triglyceride Levels. *Circ Cardiovasc Genet* 2014
 30. Parsa,A, Brown,E, Weir,MR, Fink,JC, Shuldiner,AR, Mitchell,BD, McArdle,PF: Genotype-based changes in serum uric acid affect blood pressure. *Kidney Int* 81:502-507, 2012
 31. Sedaghat,S, Pazoki,R, Uitterlinden,AG, Hofman,A, Stricker,BH, Ikram,MA, Franco,OH, Dehghan,A: Association of uric acid genetic risk score with blood pressure: the Rotterdam study. *Hypertension* 64:1061-1066, 2014
 32. Mallamaci,F, Testa,A, Leonardis,D, Tripepi,R, Pisano,A, Spoto,B, Sanguedolce,MC, Parlongo,RM, Tripepi,G, Zoccali,C: A polymorphism in the major gene regulating serum uric acid associates with clinic SBP and the white-coat effect in a family-based study. *J Hypertens* 32:1621-1628, 2014
 33. Pradhan,AD, Manson,JE, Rifai,N, Buring,JE, Ridker,PM: C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 286:327-334, 2001
 34. DeBosch,BJ, Kluth,O, Fujiwara,H, Schurmann,A, Moley,K: Early-onset metabolic syndrome in mice lacking the intestinal uric acid transporter SLC2A9. *Nat Commun* 5:4642, 2014
 35. Johnson,RJ, Perez-Pozo,SE, Sautin,YY, Manitius,J, Sanchez-Lozada,LG, Feig,DI, Shafiu,M, Segal,M, Glassock,RJ, Shimada,M, Roncal,C, Nakagawa,T: Hypothesis: could excessive fructose intake and uric acid cause type 2 diabetes? *Endocr Rev* 30:96-116, 2009
 36. Holmes,MV, Asselbergs,FW, Palmer,TM, Drenos,F, Lanktree,MB, Nelson,CP, Dale,CE, Padmanabhan,S, Finan,C, Swerdlow,DI, Tragante,V, Van Iperen,EP, Sivapalaratnam,S, Shah,S, Elbers,CC, Shah,T, Engmann,J, Giambartolomei,C, White,J, Zabaneh,D, Sofat,R, McLachlan,S, Doevendans,PA, Balmforth,AJ, Hall,AS, North,KE, Almqvera,B, Hoogetveen,RC, Cushman,M, Fornage,M, Patel,SR, Redline,S, Siscovick,DS, Tsai,MY, Karczewski,KJ, Hofker,MH, Verschuren,WM, Bots,ML, van der Schouw,YT, Melander,O, Dominiczak,AF, Morris,R, Ben-Shlomo,Y, Price,J, Kumari,M, Baumert,J, Peters,A, Thorand,B, Koenig,W, Gaunt,TR, Humphries,SE, Clarke,R, Watkins,H, Farrall,M, Wilson,JG, Rich,SS, de Bakker,PI, Lange,LA, Davey Smith,G, Reiner,AP, Talmud,PJ, Kivimaki,M, Lawlor,DA, Dudbridge,F,

- Samani,NJ, Keating,BJ, Hingorani,AD, Casas,JP: Mendelian randomization of blood lipids for coronary heart disease. *Eur Heart J* 2014
37. Ichida,K, Matsuo,H, Takada,T, Nakayama,A, Murakami,K, Shimizu,T, Yamanashi,Y, Kasuga,H, Nakashima,H, Nakamura,T, Takada,Y, Kawamura,Y, Inoue,H, Okada,C, Utsumi,Y, Ikebuchi,Y, Ito,K, Nakamura,M, Shinohara,Y, Hosoyamada,M, Sakurai,Y, Shinomiya,N, Hosoya,T, Suzuki,H: Decreased extra-renal urate excretion is a common cause of hyperuricemia. *Nat Commun* 3:764, 2012
 38. Davey Smith,G: Random allocation in observational data: how small but robust effects could facilitate hypothesis-free causal inference. *Epidemiology* 22:460-463, 2011
 39. Billings,LK, Florez,JC: The genetics of type 2 diabetes: what have we learned from GWAS? *Ann N Y Acad Sci* 1212:59-77, 2010
 40. Voight,BF, Scott,LJ, Steinthorsdottir,V, Morris,AP, Dina,C, Welch,RP, Zeggini,E, Huth,C, Aulchenko,YS, Thorleifsson,G, McCulloch,LJ, Ferreira,T, Grallert,H, Amin,N, Wu,G, Willer,CJ, Raychaudhuri,S, McCarroll,SA, Langenberg,C, Hofmann,OM, Dupuis,J, Qi,L, Segre,AV, van,HM, Navarro,P, Ardlie,K, Balkau,B, Benediktsson,R, Bennett,AJ, Blagieva,R, Boerwinkle,E, Bonnycastle,LL, Bengtsson,BK, Bravenboer,B, Bumpstead,S, Burt,NP, Charpentier,G, Chines,PS, Cornelis,M, Couper,DJ, Crawford,G, Doney,AS, Elliott,KS, Elliott,AL, Erdos,MR, Fox,CS, Franklin,CS, Ganser,M, Gieger,C, Grarup,N, Green,T, Griffin,S, Groves,CJ, Guiducci,C, Hadjadj,S, Hassanali,N, Herder,C, Isomaa,B, Jackson,AU, Johnson,PR, Jorgensen,T, Kao,WH, Klopp,N, Kong,A, Kraft,P, Kuusisto,J, Lauritzen,T, Li,M, Lieve,se,A, Lindgren,CM, Lyssenko,V, Marre,M, Meitinger,T, Midthjell,K, Morken,MA, Narisu,N, Nilsson,P, Owen,KR, Payne,F, Perry,JR, Petersen,AK, Platou,C, Proenca,C, Prokopenko,I, Rathmann,W, Rayner,NW, Robertson,NR, Rocheleau,G, Roden,M, Sampson,MJ, Saxena,R, Shields,BM, Shrader,P, Sigurdsson,G, Sparso,T, Strassburger,K, Stringham,HM, Sun,Q, Swift,AJ, Thorand,B, Tichet,J, Tuomi,T, van Dam,RM, van Haefte,TW, van,HT, van Vliet-Ostapchouk,JV, Walters,GB, Weedon,MN, Wijmenga,C, Witteman,J, Bergman,RN, Cauchi,S, Collins,FS, Gloyn,AL, Gyllenstein,U, Hansen,T, Hide,WA, Hitman,GA, Hofman,A, Hunter,DJ, Hveem,K, Laakso,M, Mohlke,KL, Morris,AD, Palmer,CN, Pramstaller,PP, Rudan,I, Sijbrands,E, Stein,LD, Tuomilehto,J, Uitterlinden,A, Walker,M, Wareham,NJ, Watanabe,RM, Abecasis,GR, Boehm,BO, Campbell,H, Daly,MJ, Hattersley,AT, Hu,FB, Meigs,JB, Pankow,JS, Pedersen,O, Wichmann,HE, Barroso,I, Florez,JC, Frayling,TM, Groop,L, Sladek,R, Thorsteinsdottir,U, Wilson,JF, Illig,T, Froguel,P, van Duijn,CM, Stefansson,K, Altshuler,D, Boehnke,M, McCarthy,MI: Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. *Nat Genet* 42:579-589, 2010
 41. Vitart,V, Rudan,I, Hayward,C, Gray,NK, Floyd,J, Palmer,CN, Knott,SA, Kolcic,I, Polasek,O, Graessler,J, Wilson,JF, Marinaki,A, Riches,PL, Shu,X, Janicijevic,B, Smolej-Narancic,N, Gorgoni,B, Morgan,J, Campbell,S, Biloglav,Z, Barac-Lauc,L, Pericic,M, Klaric,IM, Zgaga,L, Skaric-Juric,T, Wild,SH, Richardson,WA, Hohenstein,P, Kimber,CH, Tenesa,A, Donnelly,LA, Fairbanks,LD, Aringer,M, McKeigue,PM, Ralston,SH, Morris,AD, Rudan,P, Hastie,ND, Campbell,H, Wright,AF: SLC2A9 is a newly identified urate transporter influencing serum urate concentration, urate excretion and gout. *Nat Genet* 40:437-442, 2008
 42. Caulfield,MJ, Munroe,PB, O'Neill,D, Witkowska,K, Charchar,FJ, Doblado,M, Evans,S, Eyheramendy,S, Onipinla,A, Howard,P, Shaw-Hawkins,S, Dobson,RJ, Wallace,C, Newhouse,SJ, Brown,M, Connell,JM, Dominiczak,A, Farrall,M, Lathrop,GM, Samani,NJ, Kumari,M, Marmot,M, Brunner,E, Chambers,J, Elliott,P, Kooner,J, Laan,M, Org,E, Veldre,G, Viigimaa,M, Cappuccio,FP, Ji,C, Iacone,R, Strazzullo,P, Moley,KH, Cheeseman,C: SLC2A9 is a high-capacity urate transporter in humans. *PLoS Med* 5:e197, 2008

Table 1. Baseline characteristics of subcohort participants and incident type 2 diabetes cases of the EPIC-InterAct study*

	Subcohort	Type 2 diabetes
Age, years	52 (10)	55 (8)
Male	65	53
Current smoking	25	25
Low educational level	40	53
Physically inactive	59	66
Alcohol consumption, g/d, median (IQR)	5 (1, 16)	4 (0.4, 17)
BMI, kg/m ²	26.0 (4.3)	30.0 (4.8)
Systolic blood pressure, mmHg	131 (20)	143 (20)
Diastolic blood pressure, mmHg	81 (11)	87 (11)
Prevalent hypertension	19	39
Uric acid, µmol/L	280 (77)	333 (83)
Triglycerides mmol/L, median (IQR)	1.1 (0.8, 1.6)	1.7 (1.2, 2.5)
eGFR, mL/min/1.73m ²	100 (20)	95 (20)
Non-HDL cholesterol, mmol/L	4.4 (1.2)	5.0 (1.2)
Non-fasting glucose, mmol/L	5.0 (1.3)	6.4 (2.6)
HbA1c, % (mmol/mol)	5.5 [0.5] (36 [5])	6.2 [1.0] (44 [11])

* N = 10,235 subcohort participants and 7,319 incident type 2 diabetes cases;
values are mean (SD) or %, unless otherwise indicated; BMI: body mass index;
eGFR: estimated glomerular filtration rate; HDL: high-density lipoproteins.

Table 2. Observational and instrumental variable estimates for the association of circulating uric acid concentrations with incident type 2 diabetes*

Analysis	Diabetes cases, N	HR (95%CI) per 59.48 μmol/L (1 mg/dL) increase in circulating uric acid
Observational		
Adjusted for center, age and sex	10,576	1.51 (1.42, 1.62)
Adjusted for center, age, sex, BMI	10,576	1.25 (1.18, 1.33)
Multivariable model†	10,576	1.20 (1.11, 1.30)
Instrumental variable using InterAct		
Adjusted for center	7,319	1.01 (0.87, 1.16)
Adjusted for center, age, sex and BMI	7,319	0.96 (0.76, 1.20)
Instrumental variable using InterAct and DIAGRAM		OR (95%CI) per 59.48 μmol/L (1 mg/dL) increase in circulating uric acid
Combined analysis	41,508	0.99 (0.92, 1.06)

* For observational associations, N = 24,265 with 10,576 incident type 2 diabetes cases, estimates were pooled HR (95%CI) derived from random effects meta-analysis. For instrumental variable associations in InterAct, N = 17,118 with 7,319 incident type 2 diabetes cases, estimates were derived from two stage control function estimator approach analysis, and were pooled with random effects meta-analysis. For instrumental variable association using InterAct and DIAGRAM, N= 41,508 diabetes cases, and 123,974 controls. † Adjusted for study center, sex, age (as underlying time scale), BMI, systolic blood pressure, prevalent hypertension, nonHDL cholesterol (total – HDL cholesterol), triglycerides, eGFR, alcohol consumption, smoking status, highest educational level, and level of physical activity.

Table 3. Associations of individual uric acid related SNPs with circulating uric acid and incident type 2 diabetes

Gene	Chr	SNP	Uric acid raising / other allele	Beta (95%CI) for uric acid concentrations *	P-value †	HR (95%CI) for incident diabetes ‡
GCKR	2	rs780094	T/C	0.05 (0.02, 0.09)	0.01	0.98 (0.93, 1.03)
SLC2A9	4	rs734553	T/G	0.36 (0.32, 0.40)	< 0.001	1.02 (0.95, 1.09)
ABCG2	4	rs2231142	T/G	0.19 (0.13, 0.25)	< 0.001	0.93 (0.86, 1.01)
LRRC16A	6	rs742132	A/G	0.04 (0.001, 0.08)	0.04	1.00 (0.95, 1.06)
RREB1	6	rs675209	T/C	0.08 (0.04, 0.12)	< 0.001	1.03 (0.98, 1.08)
SLC16A9	10	rs12356193	A/G	0.06 (0.01, 0.11)	0.01	1.03 (0.97, 1.09)
SLC22A11	11	rs17300741	A/G	0.09 (0.05, 0.12)	< 0.001	1.00 (0.96, 1.05)
PDZK1	1	rs12129861	G/A	0.03 (0.004, 0.08)	0.03	1.04 (0.97, 1.12)
SLC17A1	6	rs1183201	T/A	0.07 (0.04, 0.11)	< 0.001	0.97 (0.93, 1.01)
SLC22A12	11	rs505802	C/T	0.05 (0.01, 0.09)	0.01	1.00 (0.91, 1.09)
INHBC	12	rs1106766	C/T	0.06 (0.02, 0.11)	0.01	1.07 (1.01, 1.13)
ORC4L	2	rs2307394	C/T	0.03 (-0.01, 0.06)	0.15	0.99 (0.93, 1.05)
SFMBT1	3	rs6770152	G/T	0.05 (0.01, 0.09)	0.01	1.06 (1.00, 1.13)
VEGFA	6	rs729761	G/T	0.07 (0.03, 0.11)	< 0.01	0.92 (0.87, 0.97)
BAZ1B	7	rs1178977	A/G	0.05 (0.01, 0.10)	0.02	1.00 (0.92, 1.09)

PRKAG2	7	rs10480300	T/C	0.06 (0.03, 0.10)	0.001	1.00 (0.95, 1.05)
STC1	8	rs17786744	G/A	0.04 (0.01, 0.08)	0.02	0.97 (0.93, 1.02)
OVOL1	11	rs642803	C/T	0.03 (-0.01, 0.06)	0.16	1.00 (0.95, 1.06)
ATXN2	12	rs653178	C/T	0.03 (-0.01, 0.06)	0.16	1.00 (0.95, 1.06)
UBE2Q2	15	rs1394125	A/G	0.003 (-0.03, 0.04)	0.86	0.99 (0.94, 1.03)
IGF1R	15	rs6598541	A/G	0.07 (0.03, 0.10)	0.001	1.03 (0.98, 1.08)
NFAT5	16	rs7193778	C/T	0.06 (0.01, 0.12)	0.02	1.02 (0.95, 1.09)
MAF	16	rs7188445	G/A	0.03 (-0.01, 0.07)	0.16	0.98 (0.92, 1.04)
BCAS3	17	rs2079742	T/C	0.02 (-0.02, 0.07)	0.30	1.01 (0.96, 1.08)

* Beta obtained from linear regression with uric acid modeled per 59.48 $\mu\text{mol/L}$ (1 mg/dL) increase, and SNPs modeled per uric acid increasing allele (additive model), adjusted for study center, among 10,235 subcohort participants; † P-value for association uric acid related SNPs with uric acid concentrations; ‡ HR and 95%CI obtained from random effects meta-analysis using modified Cox regression, adjusted for study center, among 17,118 participants of which 7,319 were incident diabetes cases.