Habitual coffee intake, genetic polymorphisms, and type 2 diabetes

Jae Kyung Lee¹, Kyunga Kim², Younjin Ahn³, Mihi Yang⁴ and Jung Eun Lee¹

¹Department of Food and Nutrition, Sookmyung Women's University, Cheongpa-ro 47-gil 100, Yongsan-gu, Seoul 140-742, Republic of Korea, ²Biostatistics and Clinical Epidemiology Center, Samsung Medical center, 50 Ilwon-dong, Gangnam-gu, Seoul 135-170, Republic of Korea, ³Division of Cardiovascular and Rare Disease, National Institute of Health, Centers of Biomedical Sciences, Center for Disease Control and Prevention, Chungcheongbuk-do, Republic of Korea and ⁴Research Center for Cell Fate control, College of Pharmacy, Sookmyung Women's University, Cheongpa-ro 47-gil 100, Yongsan-gu, Seoul 140-742, Republic of Korea

Correspondence should be addressed to J E Lee
Email
junglee@sm.ac.kr

Abstract

Background: The association between coffee intake and type 2 diabetes may be modulated by common genetic variation. **Objective:** The purpose of this study was to examine the association between habitual coffee intake and the risk of type 2 diabetes and to determine whether this association varied by genetic polymorphisms related to type 2 diabetes in Korean adults.

Design and methods: A population-based cohort study over a follow-up of 4 years was conducted. A total of 4077 Korean men and women aged 40–69 years with a normal glucose level at baseline were included. Coffee intake was assessed using a validated food frequency questionnaire, and incident type 2 diabetes or prediabetes was defined by oral glucose tolerance test or fasting blood glucose test. The genomic DNA samples were genotyped with the Affymetrix Genome-Wide Human SNP Array 5.0, and nine single-nucleotide polymorphisms related to type 2 diabetes in East Asian populations were extracted.

Results: A total of 120 cases of type 2 diabetes and 1128 cases of prediabetes were identified. After adjustment for potential confounding factors, we observed an inverse association, but without any clear linear trend, between coffee intake and the combined risk of type 2 diabetes and prediabetes. We found that inverse associations between habitual coffee intake and the combined risk of type 2 diabetes and prediabetes were limited to those with the T-allele (GT/TT) of rs4402960 in *IGF2BP2*, those with the G-allele (GG/GC) of rs7754840 in *CDKAL1*, or those with CC of rs5215 in *KCNJ11*.

Conclusion: We found a lower risk of prediabetes and type 2 diabetes combined with coffee intake among individuals with the GT/TT of *IGF2BP2* rs4402960, GG/GC of *CDKAL1* rs7754840, or CC of *KCNJ11* rs5215, which are known to be related to type 2 diabetes in East Asians.

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Introduction

Coffee is the most widely consumed beverage in the world. Data from the Food and Agriculture Organization (FAO) indicate that per capita coffee supply in Korea has been steadily rising over the last three decades, with estimates of 1 g/capita/day in 1981, 3 g/capita/day in 1992, and 4–5 g/capita/day in the 2000s (1).

Epidemiologic studies have shown that coffee intake decreases the risk of some chronic diseases, including Alzheimer's disease (2), Parkinson's disease (3), colorectal

cancer (4), and heart failure (5). In particular, the association between coffee intake and the risk of type 2 diabetes has been long studied, supporting the hypothesis that intake of both caffeinated and decaffeinated coffee may reduce the risk of type 2 diabetes (6, 7, 8). The inverse association between coffee intake and type 2 diabetes has been observed in the Western population and in the Chinese (9) and Japanese (10, 11, 12) populations. However, to our knowledge, there have been no

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epidemiologic studies on coffee intake and type 2 diabetes in Korea, despite the high prevalence of type 2 diabetes in Korea (11.9% among men and 7.6% among women in 2011) (13). The Korea National Health and Nutrition Examination Survey (KNHANES) reported that 23.8% of men and 14.9% of women had impaired fasting glucose (IFG) in 2011 (13).

Potential mechanisms have been suggested to explain the inverse association between coffee intake and the risk of type 2 diabetes. Coffee contains many bioactive components, including caffeine, phenolic compounds, minerals, fibers, and lignans, which may prevent the risk of type 2 diabetes (14). Caffeine has been suggested to improve glucose metabolism possibly through increase in thermogenesis (15). Antioxidants in coffee, such as chlorogenic acid and quinides, have been proposed to have beneficial effects on glucose metabolism in animal studies (16, 17).

Several genetic epidemiologic studies have identified genetic polymorphisms related to type 2 diabetes in East Asians. Among more than 60 genetic variants that have been shown to be associated with type 2 diabetes in candidate gene studies and genome-wide association studies (GWASs) (18), the significant associations with genetic variants initially discovered in Europeans have been replicated in East Asians in or near the glucokinase regulator (*GCKR*), insulin-like growth factor 2 binding protein 2 (*IGF2BP2*), peroxisome proliferator-activated receptor gamma (*PPARG*), cyclin-dependent kinase 5 regulatory subunit-associated protein-1-like 1 (*CDKAL1*), juxtaposed with another zinc finger gene 1 (*JAZF1*), cyclin-dependent kinase inhibitor 2A/B (*CDKN2A/B*), potassium inwardly rectifying channel, subfamily J, member 11 (*KCNJ11*), and fat mass and obesity associated (*FTO*) genes, and genetic variants newly discovered in East Asians have been replicated in Europeans in or near the *KCNQ1*, *C2CD4A/B*, sprouty 2 (*SPRY2*), and *FITM2/R3HDM1/HNF4A* genes (18).

Because both genetic and environmental factors are involved in type 2 diabetes susceptibility, gene–environment interaction in relationship with diabetes, especially diet and common genetic variations, may be of great interest. Given previous reports of the associations of coffee intake and common polymorphism in relationship with the risk of diabetes, we hypothesized that the association for coffee intake could be modified by genetic polymorphisms. Therefore, in this prospective study, we examined the association between coffee intake, genetic polymorphisms related to type 2 diabetes, and the development of type 2 diabetes and prediabetes in Korean adults.

Subjects and methods

Study population

This community-based prospective study, the Korean Association Resource (KARE) study, initially enrolled 5018 and 5020 participants aged between 40 and 69 years from rural Ansung and urban Ansan respectively. These participants have been examined biennially since 2001 through epidemiologic surveys, physical examinations, and laboratory tests. Among the 10 038 participants, genomic DNA samples of 8842 participants were successfully genotyped after performing genotype calling and quality control processes. A total of 6544 participants whose DNA samples were genotyped underwent health examinations at both baseline in 2001 and during a second follow-up in 2005.

Among the 6544 men and women, we excluded participants who had type 2 diabetes or prediabetes at baseline ($n=2065$); a history of type 2 diabetes ($n=65$); cardiovascular disease, including myocardial infarction, heart failure, coronary heart disease, and stroke ($n=108$); tumor ($n=34$) at baseline; unreasonable energy intake (beyond 3 S.D.s of the log-transformed energy intake) ($n=189$); or did not provide information on coffee intake ($n=6$). As a result, a total of 4077 participants (1961 men and 2116 women) were included in the analyses. This study was approved by the Institutional Review Board of Sookmyung Women's University.

Assessment of coffee intake and other risk factors

Coffee intake was assessed at baseline using a validated 103-item semi-quantitative food frequency questionnaire (FFQ). This FFQ was developed for the Korean Genome and Epidemiology Study (KoGES) and validated by comparing the nutrient intakes from the 3-day diet records with FFQ (19, 20). In the FFQs, the participants were asked how often on average during a period of 1 year they had consumed coffee (almost none, 1 serving/month, 2–3 servings/month, 1–2 servings/week, 3–4 servings/week, 5–6 servings/week, 1 serving/day, 2 servings/day, or 3 servings/day) and how many cups of coffee they drank per serving (0.5, 1, or 2 cups). The amount of vegetables, fruit, red meat, and dairy food consumed (g/day) was calculated by summing the amounts of the relevant food items consumed; the amount of each food item was estimated by multiplying the serving units consumed per day by the portion size per unit.

The participants' demographic factors, past medical history, smoking status, alcohol intake, and physical

activity were determined using structured questionnaires administered by trained interviewers. Anthropometric measurements were obtained by trained health professionals. Height and weight were measured while the participants were wearing light clothing with no shoes. BMI was calculated by dividing weight (kg) by height squared (m^2).

Case ascertainment

All of the participants underwent a 2-h 75 g oral glucose tolerance test (OGTT) at baseline and at a 4-year follow-up, and blood samples were drawn at 0, 60, and 120 min after 8–14 h of overnight fasting. The concentrations of fasting plasma glucose (FPG) and 2-h post-load glucose (2-h PG) were measured by the hexokinase method (ADVIA 1650; Bayer, Inc.). At baseline and during follow-up, cases of type 2 diabetes and prediabetes were defined according to the American Diabetes Association (ADA) criteria (21). The cases of type 2 diabetes were defined if participants had one of the following conditions: i) ≥ 126 mg/dl (≥ 7.0 mmol/l) of FPG; ii) ≥ 200 mg/dl (≥ 11.1 mmol/l) of 2-h PG; or iii) had been treated for diabetes with insulin therapy or oral hypoglycemic medication. The cases of prediabetes were defined if participants had IFG (100–125 mg/dl of FPG) or impaired glucose tolerance (140–199 mg/dl of 2-h PG).

Genotyping assays

The genomic DNA samples isolated from the peripheral blood of participants were directly genotyped with the Affymetrix Genome-Wide Human SNP Array 5.0. Bayesian robust linear modeling was performed with the Mahalanobis Distance (BRLMM) Genotyping Algorithm (Affymetrix, Inc., Santa Clara, CA, USA) using 500 568 single-nucleotide polymorphisms (SNPs). After sample and SNP quality control, 8842 samples and 352 228 SNPs remained. Detailed exclusion criteria for samples and SNPs have been described in a previous study (22).

A few GWAS and candidate gene studies found that the genetic loci related to type 2 diabetes in East Asian populations (23) and several genetic SNPs have been confirmed by replication studies conducted in independent populations (18). In our study, we extracted nine SNPs that have been associated with type 2 diabetes in both European and East Asian populations (18); *GCKR* rs780094, *PPARG* rs1801282, *IGF2BP2* rs4402960, *CDKAL1* rs7754840, *JAZF1* rs864745, *CDKN2A/B* rs10811661, *KCNJ11* rs5215, *SPRY2* rs1359790, and *FTO* rs8050136.

Statistical analyses

We calculated the mean, s.d., and proportion to examine the baseline characteristics according to coffee intake. We used multivariate logistic regression models to assess the associations with the combined risk of prediabetes and type 2 diabetes. We calculated odds ratios (ORs) and 95% CIs with adjustment for age, sex, residential area (Ansung or Ansan), BMI (kg/m^2 , continuous), total energy intake (kcal/day, continuous), smoking status (never smoker and ever smoker), alcohol intake (nondrinker and drinker), educational level (≤ 6 , 7 to <9 , and ≥ 9 years), vigorous physical activity (min/day), fruit and vegetable intake (<300 , 300 to <450 , 450 to <600 , and ≥ 600 g/day), red meat intake (<15 , 15 to <30 , 30 to <45 , and ≥ 45 g/day), and dairy food intake (0, 0 to <50 , 50 to <100 , and ≥ 100 g/day) at baseline. Adjustment for finer categories of variables such as smoking and alcohol for men (smoking; <20 or ≥ 20 pack-years among past or current smokers, and alcohol; <10 , 10 to <30 , and 30 g/day) did not appreciably change the results. To test for linear trends across categories of coffee intake, we included the median of each category of coffee intake in the model as a continuous variable.

Table 1 Baseline characteristics of the study population according to coffee intake. Mean $\pm$ s.d. for continuous variables.

	Coffee intake	
	Nondrinker	Drinker
No. of type 2 diabetes/prediabetes/noncases	25/235/606	95/893/2223
Age (years)	53.6 $\pm$ 8.6	50.3 $\pm$ 8.3
Sex (men, %)	34.8	51.7
Residential area (rural, %)	62.8	46.6
BMI (kg/m^2)	23.9 $\pm$ 3.0	24.5 $\pm$ 3.0
Marital status (married, %)	89.3	92.7
Family history of diabetes (yes, %)	7.6	10.3
Educational level (%)		
≤ 6 years	44.2	25.7
7 to <9 years	23.2	23.6
≥ 9 years	32.6	50.7
Smoking status (%)		
Never smoker	74.6	55.8
Ever smoker	25.4	44.2
Alcohol intake (%)		
Nondrinker	61.4	42.1
Drinker	38.6	57.9
Vigorous physical activity (min/day)	107.7 $\pm$ 141.7	82.6 $\pm$ 128.5
Total energy intake (kcal/day)	1834.1 $\pm$ 640.4	1949.9 $\pm$ 590.3
Red meat intake (g/day)	39.3 $\pm$ 50.9	50.5 $\pm$ 50.4
Fruit and vegetable intake (g/day)	576.4 $\pm$ 409.1	541.3 $\pm$ 351.6
Dairy food intake (g/day)	104.7 $\pm$ 128.6	107.2 $\pm$ 125.4

We evaluated the interaction effects of age (median age <49 or ≥49 years), smoking status (never smoker or ever smoker), BMI (<25 or ≥25 kg/m²), physical activity (yes or no), alcohol intake (nondrinker or drinker), and genotypes related to type 2 diabetes. To test for differences, we compared models with and without cross-product terms using a likelihood ratio test.

All analyses were performed using SAS Software (version 9.3, SAS Institute, Cary, NC, USA). Significance was defined as a *P* value <0.05 in two-sided tests.

Results

Out of 4077 participants with a normal glucose level at baseline, a total of 120 participants developed type 2 diabetes and 1128 participants developed prediabetes during the 4-year follow-up period. Table 1 shows the baseline characteristics according to coffee intake. Compared with nondrinkers, coffee drinkers were more likely to be male, younger, married, educated, alcohol drinkers, and ever smokers. However, coffee drinkers were less likely to be physically active compared with nondrinkers. Higher intakes of energy and red meat were observed among coffee drinkers compared with nondrinkers.

Table 2 presents the ORs and 95% CIs for prediabetes and type 2 diabetes combined according to coffee intake. We found a lower risk of prediabetes and type 2 diabetes combined with two or more cups of coffee per day, but less than two cups did not confer the benefit; compared with almost none, the multivariate-adjusted ORs (95% CIs) were 0.80 (0.65–0.98; *P* trend=0.05) for two or more cups per day of coffee intake. However, the associations were not statistically significant for either men or women. When we compared coffee drinkers with nondrinkers, the multivariate-adjusted OR (95% CI) was 0.89 (0.74–1.06) for risk of prediabetes and type 2 diabetes combined. Adjustment for family history of type 2 diabetes did not substantially alter these ORs (data not shown). Stratification between prediabetes and type 2 diabetes as outcomes showed that the multivariate-adjusted ORs (95% CIs) were 0.89 (0.75–1.07) for the risk of prediabetes and 0.83 (0.52–1.32) for the risk of type 2 diabetes (Supplementary Table 1, see section on supplementary data given at the end of this article).

We performed interaction analyses to examine whether the association of coffee intake with type 2 diabetes and prediabetes combined varied according to age, BMI, smoking status, physical activity, and alcohol intake. The inverse association did not vary significantly

Table 2 Odds ratios (ORs) and 95% CIs for the combined risk of prediabetes and type 2 diabetes according to coffee intake.

	Coffee intake					<i>P</i> trend
	Nondrinker	Drinker	0 cup/day	0 to <1 cup/day	1 to <2 cups/day	≥2 cups/day
Men						
No. of type 2 diabetes/prediabetes/noncases			11/94/196	18/122/319	24/157/292	20/206/502
Type 2 diabetes and prediabetes						
Age-adjusted ORs (95% CIs)			1.00 (ref.)	0.82 (0.60–1.12)	1.16 (0.85–1.57)	0.84 (0.63–1.12)
Multivariate-adjusted ORs ^a (95% CIs)			1.00 (ref.)	0.80 (0.58–1.10)	1.01 (0.74–1.39)	0.75 (0.56–1.02)
Women						
No. of type 2 diabetes/prediabetes/noncases			14/141/410	10/129/379	15/167/394	8/112/337
Type 2 diabetes and prediabetes						
Age-adjusted ORs (95% CIs)			1.00 (ref.)	1.00 (0.76–1.31)	1.28 (0.99–1.65)	1.01 (0.76–1.34)
Multivariate-adjusted ORs ^a (95% CIs)			1.00 (ref.)	0.90 (0.68–1.20)	0.99 (0.75–1.30)	0.87 (0.65–1.18)
Men and women combined						
No. of type 2 diabetes/prediabetes/noncases	25/235/606	95/893/2223	25/235/606	28/251/698	39/324/686	28/318/839
Type 2 diabetes and prediabetes						
Age- and sex-adjusted ORs (95% CIs)	1.00 (ref.)	1.01 (0.86–1.20)	1.00 (ref.)	0.91 (0.75–1.12)	1.23 (1.01–1.49)	0.92 (0.75–1.12)
Multivariate-adjusted ORs ^a (95% CIs)	1.00 (ref.)	0.89 (0.74–1.06)	1.00 (ref.)	0.87 (0.70–1.07)	1.00 (0.82–1.23)	0.80 (0.65–0.98)

^aAdjustment for age, sex, residential area (Ansung or Ansan), BMI (kg/m², continuous), total energy intake (kcal/day, continuous), smoking status (never smoker and ever smoker), alcohol intake (nondrinker and drinker), educational level (≤6, 7 to <9, and ≥9 years), vigorous physical activity (min/day), fruit and vegetable intake (<300, 300 to <450, 450 to <600, and ≥600 g/day), red meat intake (<15, 15 to <30, 30 to <45, and ≥45 g/day), and dairy food intake (0, 0 to <50, 50 to <100, and ≥100 g/day).

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Table 3 Multivariate-adjusted odds ratios (ORs)^a and 95% CIs for the combined risk of prediabetes and type 2 diabetes according to coffee intake stratified by type 2 diabetes-related SNPs.

SNP ID (M/m)	Chr	Locus	Coffee intake		P heterogeneity
			Nondrinker	Drinker	
rs4402960 (G/T) GG	3	<i>IGF2BP2</i>	No. of cases/noncases ORs (95% CIs)	118/326 1.00 (ref.)	0.02
GT+GT			No. of cases/noncases ORs (95% CIs)	522/1164 1.06 (0.82–1.36)	
				142/280 1.00 (ref.)	
rs7754840 (G/C) GG+GC	6	<i>CDKAL1</i>	No. of cases/noncases ORs (95% CIs)	732/1708 0.78 (0.64–0.95)	0.01
CC			No. of cases/noncases ORs (95% CIs)	236/465 1.43 (0.96–2.14)	
rs5215 (T/C) TT+TC	11	<i>KCNJ11</i>	No. of cases/noncases ORs (95% CIs)	824/1862 0.95 (0.79–1.15)	0.06
CC			No. of cases/noncases ORs (95% CIs)	153/334 0.56 (0.35–0.89)	

Chr, chromosome; M, major allele; m, minor allele; SNP, single-nucleotide polymorphism.

^aAdjustment for age, sex, residential area (Ansung or Ansan), BMI (kg/m², continuous), total energy intake (kcal/day, continuous), smoking status (never smoker and ever smoker), alcohol intake (nondrinker and drinker), educational level (≤ 6 , 7 to < 9 , and ≥ 9 years), vigorous physical activity (min/day), fruit and vegetable intake (< 300 , 300 to < 450 , 450 to < 600 , and ≥ 600 g/day), red meat intake (< 15 , 15 to < 30 , 30 to < 45 , and ≥ 45 g/day), and dairy food intake (0, 0 to < 50 , 50 to < 100 , and ≥ 100 g/day).

according to age, BMI, smoking status, physical activity, or alcohol intake (P heterogeneity ≥ 0.17 ; data not shown).

We examined whether the association between coffee intake and the combined risk of prediabetes and type 2 diabetes modified by genotypes of SNPs related to type 2 diabetes (Table 3 and Supplementary Table 2, see section on supplementary data given at the end of this article). The inverse association differed by polymorphisms of rs4402960 in *IGF2BP2*, rs7754840 in *CDKAL1*, and rs5215 in *KCNJ11*. A statistically significant inverse association was observed in the carriers of the *IGF2BP2* rs4402960 T-allele (GT/TT) compared with noncarriers (GG) (P heterogeneity=0.02; OR (95% CI) was 0.73 (0.57–0.94) comparing coffee drinking with almost none among those with T-allele. For *CDKAL1* rs7754840, a pattern of inverse association between coffee intake and type 2 diabetes and prediabetes combined was limited to carriers of the G-allele (GG/GC) (P heterogeneity=0.01). The participants with CC of *KCNJ11* rs5215 had a lower risk of prediabetes and type 2 diabetes with coffee intake (OR=0.56; 95% CI=0.35–0.89), but those with TT/TC did not (P heterogeneity=0.06). The associations did not vary at the other SNPs related to type 2 diabetes.

Discussion

We observed an inverse association, but without a clear linear trend, between coffee intake and the combined risk

of type 2 diabetes and prediabetes over a 4-year follow-up among Korean adults. Among nine SNPs, all of which have been shown to be associated with type 2 diabetes in East Asians (18), three SNPs (*IGF2BP2* rs4402960, *CDKAL1* rs7754840, and *KCNJ11* rs5215) showed a significant interaction with coffee intake in our study. We found that an inverse association between habitual coffee intake and the combined risk of prediabetes and type 2 diabetes was limited to the T-allele (GT/TT) of rs4402960 in *IGF2BP2*, the G-allele (GG/GC) of rs7754840 in *CDKAL1*, or CC of rs5215 in *KCNJ11*. These results warrant further Korean prospective studies.

Several prospective studies, conducted predominantly in Western populations (6, 7), have shown an inverse association between coffee intake and the risk of type 2 diabetes in men and/or women. A recent meta-analysis reported that one cup of coffee per day contributed to a 7% decrease in the risk of type 2 diabetes (relative risk=0.93; 95% CI=0.91–0.95) (7). In addition, similar associations were observed for Asian populations (9, 10, 11, 12). Most of these studies have demonstrated inverse associations between coffee intake and the risk of type 2 diabetes.

GWAS have successfully identified genetic variants for type 2 diabetes (23, 24) and coffee intake (25). However, evidences on gene–coffee interactions in relationship with diabetes are scarce. Given the complexity of diabetes pathogenesis, our study suggests the evidence that genetic–environmental interactions contribute to the

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development of type 2 diabetes. The T-allele, which is the risk allele of *IGF2BP2* rs4402960, was associated with type 2 diabetes, with an OR of 1.07/T-allele (P value = 9.0×10^{-3}) in East Asians (18). The *IGF2BP2* gene regulates IGF2, which is known to be involved in insulin action (26), and also decreases glucose-stimulated insulin release (27). *CDKAL1*, encoded by the *CDKAL1* gene, shares similar protein domains with CDK5 regulatory subunit-associated protein 1 (CDK5RAP1), an inhibitor of CDK5 activation. The activity of the CDK5–p35 complex is regulated in response to glucose concentration, leading to the regulation of pancreatic β -cell function (28, 29). *KCNJ11* gene encodes Kir6.2, a major subunit of the ATP-sensitive inward rectifier potassium channel that was found to play an important role in the regulation of insulin secretion by pancreatic β -cell (30). The T-allele of rs5219, which is a proxy of *KCNJ11* rs5215, was associated with impaired serum insulin response during an OGTT in human study (31). Our finding may be supported by the evidence that caffeine can inhibit the activity of ATP-sensitive potassium channel (32). The stronger inverse association between coffee intake and type 2 diabetes among individuals with specific SNP genotypes may suggest a potential interaction between coffee intake and genetic polymorphisms that partially determine type 2 diabetes development. Future studies should replicate our findings with independent populations, including both Asians and other ethnic groups.

We observed that coffee drinkers were more likely to have unhealthy lifestyle factors compared with nondrinkers, such as a higher smoking rate, lower physical activity, and higher alcohol intake. Therefore, these positive confounding factors could have overestimated the association if these had not been adjusted, and adjustment for potential confounding factors de-attenuated the association in our study.

The strength of our study lies in the fact that this is, to our knowledge, the first prospective cohort study examining the association between coffee intake and type 2 diabetes in Korea. Secondly, cases of type 2 diabetes and prediabetes were directly identified by OGTT and FPG. Therefore, we were able to identify asymptomatic participants with type 2 diabetes and minimize its underdiagnosis.

Our study had several limitations. First, because this is an observational study, we could not infer causation between coffee and diabetes. Second, the FFQ used in this study did not distinguish decaffeinated coffee from caffeinated coffee because decaffeinated coffee is not commonly consumed in Korea (33). We also could not obtain information about the types of coffee consumed in

this study (e.g., boiled coffee, filtered coffee, or instant coffee). Third, measurement errors may have occurred because information on coffee intake was obtained through interviews. Although coffee intake on the FFQ was not validated with other dietary instrument in our study, the FFQ used had reasonable validity of the nutrients (20). Fourth, we cannot exclude the possibility that residual or unmeasured confounding factors were present.

In conclusion, we found a lower risk of prediabetes and type 2 diabetes combined with coffee intake among individuals with the GT/TT of *IGF2BP2* rs4402960, GG/GC of *CDKAL1* rs7754840, or CC of *KCNJ11* rs5215, which are known to be related to type 2 diabetes in East Asians. Further clinical and experimental studies are needed to explore the causal mechanisms of coffee for the development of type 2 diabetes, and replication studies are warranted in other populations.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-14-0805>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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