A THESIS FOR THE DEGREE OF
MASTER OF SCIENCE IN FOOD AND NUTRITION

Coffee consumption, genetic polymorphisms, and the risk of type 2 diabetes mellitus: a pooled analysis of four prospective cohort studies

커피 섭취, 유전적 다형성과 제2형 당뇨병과의 연관성: 한국인 코호트 통합분석

August, 2020

Department of Food and Nutrition
Graduate School
Seoul National University
An Na Kim

Coffee consumption, genetic polymorphisms, and the risk of type 2 diabetes mellitus: a pooled analysis of four prospective cohort studies

커피 섭취, 유전적 다형성과 제2형 당뇨병과의 연관성: 한국인 코호트 통합분석

지도교수 이 정 은
이 논문을 식품영양학석사 학위논문으로 제출함

2020 년 5 월

서울대학교 대학원
식품영양학과
김 안 나

김안나의 석사 학위논문을 인준함
2020 년 7 월

위 원 장 _____ (인)
부 위 원 장 _____ (인)
위 원 _____ (인)

Abstract

Coffee consumption, genetic polymorphisms, and the risk of type 2 diabetes mellitus: a pooled analysis of four prospective cohort studies

An Na Kim
Department of Food and Nutrition
The Graduate School
Seoul National University

Diabetes mellitus is a global health problem. Coffee consumption has drawn attention in relation to type 2 diabetes prevention because of its widespread consumption and the effects of polyphenol compounds. Epidemiological meta-analyses have shown an inverse association between coffee consumption and the risk of type 2 diabetes. In addition, the association of coffee consumption and the risk of type 2 diabetes may vary by genetic variants. This study aims to address the question of whether the incidence of type 2 diabetes is related to consumption of coffee, and whether this relationship is modified by 5 single nucleotide polymorphisms (SNPs) related to type 2 diabetes (*CDKAL1* rs7756992, *CDKN2A/B* rs10811661, *KCNJ11* rs5215, *KCNQ1* rs163184, and *PEPD* rs3786897) in four Korean prospective cohort

studies. A pooled analysis of 4 Korean prospective studies (The Health Examinees (HEXA) study, the Cardiovascular Disease Association Study (CAVAS), the Korea Association Resource (KARE) study, and the Healthy Twin (TWIN) study) included 71,527 participants with median follow-up periods ranging between 2-13 years was performed. To estimate the pooled odds ratios (ORs) of the four prospective cohort studies, the categories of coffee consumption were unified into four categories: <0.5, 0.5 to <1, 1 to <2, ≥3 cups per day. The odds ratios (ORs) and 95% confidence intervals (CIs) for type 2 diabetes were calculated using logistic regression models. The ORs were combined using a fixed or random effects model depending on the heterogeneity across the studies. Subgroup analyses were additionally performed to examine whether the associations of coffee consumption with type 2 diabetes varied by age, sex, BMI, smoking status, alcohol drinking, and type 2 diabetes susceptibility genes using a meta-regression model. Test for non-linearity of the association was performed using restricted cubic splines. A total of 4,600 incident type 2 diabetes were diagnosed among participants during the follow-up. An inverse association between coffee consumption and risk of type 2 diabetes was observed. Compared to 0 to <0.5 cups/day of coffee consumption, pooled ORs (95% CIs) were 1.02 (0.91-1.14) for 0.5 to <1 cups/day of coffee consumption, 0.97 (0.90-1.05) for 1 to <3 cups/day of coffee consumption, 0.89 (0.80-0.98) for ≥3 cups/day of coffee consumption (*p* for trend=0.01). The inverse association did not vary by polymorphisms of rs7756992 in *CDKAL1*, rs10811661 in *CDKN2A/B*, rs5215 in *KCNJ11*, rs163184 in *KCNQ1*, and rs3786897 in *PEPD* (*p* for interaction=0.56, 0.97,

0.73, 0.62, 0.68, respectively). In summary, coffee consumption was significantly associated reduced risk of type 2 diabetes incidence. Statistically significant interactions of coffee consumption were not observed for 5 SNPs related to type 2 diabetes (*CDKAL1* rs7756992, *CDKN2A/B* rs10811661, *KCNJ11* rs5215, *KCNQ1* rs163184, and *PEPD* rs3786897) in association between coffee and the risk of type 2 diabetes. Further replication of gene and diet interaction for type 2 diabetes in Asian populations is needed.

Keyword: Coffee consumption, Type 2 diabetes, Genetic polymorphisms, Korean Genome Epidemiology Study, Pooled analysis

Student Number: 2018-23665

Contents

List of Tables

List of Figures

List of Abbreviations

BMI	Body mass index
CIs	Confidence intervals
CAVAS	Cardiovascular Disease Association Study
Chr	Chromosome
FFQ	Food frequency questionnaire
GWAS	Genome-wide association study
HEXA	The Health Examinees
KARE	Korea Association Resource
KoGES	Korean Genome and Epidemiology study
MET-h	Metabolic equivalent hours
OGTT	Oral glucose tolerance test
ORs	Odds ratios
SD	Standard deviation
SNP	Single nucleotide polymorphisms
TWIN	Healthy Twin

I. Introduction

Diabetes mellitus is a global health problem. The global age-standardized adult prevalence of diabetes was 8.3 % in 2019 and is projected to reach 9.6 % by 2045 (Saeedi et al., 2019). Type 2 diabetes is the most prevalent and accounts for 90% of all cases of diabetes mellitus (International Diabetes Federation, 2017). The prevalence of type 2 diabetes has increased during the last decade within Asian populations (Noh, 2016). The prevalence of diabetes among Korean adults aged ≥30 years increased from 9.7% to 10.4% between 2008 and 2018 (Ministry of Health and Welfare Korea Centers for Disease Control and Prevention, 2020). Type 2 diabetes can be prevented by identifying modifiable risk factors that are imperative for the prevention of type 2 diabetes. The associations of dietary behaviors (healthy dietary patterns and the alternative healthy eating index) and foods (intake of whole grains, red meat, processed meat, and sugar-sweetened beverages) with the incidence of type 2 diabetes has been examined in a meta-analysis (Neuenschwander et al., 2019).

Coffee has drawn attention in relation to type 2 diabetes prevention because of its widespread consumption and the effects of polyphenol compounds. Particularly in Korea, along with economic development, coffee consumption is steadily increasing. The average coffee consumption increased 1.08 cups/day in 2018 from 0.59 cups/day in 2001 (Ministry of Health and Welfare Korea Centers for Disease Control and Prevention, 2020). The average frequency of drinking coffee among Korean adults was 11 times/week in 2016, making coffee the most frequently consumed food

(Ministry of Health and Welfare Korea Centers for Disease Control and Prevention, 2018). Despite the high prevalence of type 2 diabetes and consumption of coffee in Korea, studies on coffee consumption and the risk of type 2 diabetes among Koreans are sparse.

Epidemiological meta-analyses have shown an inverse association between coffee consumption and the risk of type 2 diabetes (Ding, Bhupathiraju, Chen, van Dam, & Hu, 2014; Jiang, Zhang, & Jiang, 2014; van Dam & Hu, 2005). In a recent dose-response meta-analysis, the risk of type 2 diabetes decreased by 6% (RR=0.94; 95% CI=0.93–0.95) for each cup/day increase in coffee consumption (Carlström & Larsson, 2018). Several mechanisms underlying this protective effect of coffee on the risk of type 2 diabetes have been suggested. Biological components in coffee such as caffeine, chlorogenic acids, lignans, and antioxidants have been suggested to play a role in regulating insulin and glucose which influence the process of developing type 2 diabetes (Bidel et al., 2008; Costabile, Sarnsamak, & Hauge-Evans, 2018; van Dam, 2006).

In addition to lifestyle factors, genetic factors also play a role in the development of type 2 diabetes. Although genome-wide association studies (GWAS) have identified many genetic variant loci related to type 2 diabetes, these variants explain approximately 6% of the susceptibility of type 2 diabetes (Morris et al., 2012). It is important to further investigate interaction studies because its interaction by genetic variants may partly explain the remaining susceptibility of type 2 diabetes (Cornelis & Hu, 2012). Susceptibility to modifiable lifestyle factors depends on genetic factors,

which may interact with lifestyle factors (Cornelis & Hu, 2012; Dietrich et al., 2019). Identifying type 2 diabetes risk subgroups based on the type 2 diabetes susceptibility gene which may modify specific foods or nutrients, may help develop more individualized prevention strategies (Dietrich et al., 2019).

A recent trans-ethnic meta-analysis of more than 110,000 individuals, which combined GWAS data in multiple ethnic groups, including European, East Asian, South Asian, and Mexican/Mexican African individuals, has shown genetic variants related to type 2 diabetes (Diabetes Genetics Replication and Meta-analysis Consortium, Asian Genetic Epidemiology Network Type 2 Diabetes Consortium, South Asian Type 2 Diabetes Consortium, Mexican American Type 2 Diabetes Consortium, & Type 2 Diabetes Genetic Exploration by Nex-generation sequencing in muylti-Ethnic Samples Consortium, 2014). Among more than 70 genetic variants across the ethnic groups, only 4 genetic variants have been shown to be significantly ($P < 1 \times 10^{-6}$) associated with type 2 diabetes in East Asian populations and 1 genetic variant was significant in both European and East Asian populations (Diabetes Genetics Replication and Meta-analysis Consortium, Asian Genetic Epidemiology Network Type 2 Diabetes Consortium, South Asian Type 2 Diabetes Consortium, Mexican American Type 2 Diabetes Consortium, & Type 2 Diabetes Genetic Exploration by Nex-generation sequencing in muylti-Ethnic Samples Consortium, 2014).

The association of coffee consumption and the risk of type 2 diabetes was assumed that it may be modified by type 2 diabetes polymorphisms. This study addresses the

question of whether the incidence of type 2 diabetes is related to the consumption of coffee, and whether this relationship varies by type 2 diabetes susceptibility genes. In this study, the association between coffee consumption and genetic polymorphisms related to type 2 diabetes was examined in four Korean prospective cohort studies.

II. Literature review

1. Epidemiology of type 2 diabetes

Type 2 diabetes is a long-term condition that is characterized by hyperglycemia resulting from abnormal insulin secretion or insulin resistance (American Diabetes Association, 2020). The global age-standardized adult prevalence of diabetes was 8.3 % in 2019 and is projected to reach 9.6 % by 2045 (Saeedi et al., 2019). Of the world's diabetic population, Asia accounts for 60% of diabetes (Saeedi et al., 2019). Asia underwent rapid economic and epidemiologic transition, changed in dietary patterns and nutritional status (Chan et al., 2009). These have resulted in a rapid increase in the prevalence of diabetes within a relatively short period of time (Chan et al., 2009).

The prevalence of type 2 diabetes in Korea is also increasing. The age-standardized prevalence of type 2 diabetes increased from 9.7 in 2008 to 10.4 in 2018 (Figure 1) (Ministry of Health and Welfare Korea Centers for Disease Control and Prevention, 2020). In 2018, the prevalence of diabetes among women was 7.9% which was lower than those in men (12.9%) (Ministry of Health and Welfare Korea Centers for Disease Control and Prevention, 2020). Specifically, the prevalence of diabetes among adults 65 years or older was 25.1%, which was more than twice the prevalence of diabetes among adults aged 30 years or more (Ministry of Health and Welfare Korea Centers for Disease Control and Prevention, 2020).

2. Genetic polymorphisms of type 2 diabetes

It is well established that the risk of developing type 2 diabetes is linked to on both genetic and environmental factors. In spite of genome-wide association studies (GWAS) have identified many genetic variant loci related to type 2 diabetes, these variants explain approximately 6% of the susceptibility of the type 2 diabetes (Morris et al., 2012). It is important to further investigate interaction studies because its interaction by genetic variants may partly explain the remaining susceptibility of type 2 diabetes (Cornelis & Hu, 2012).

Although Asians have lower rates of overweight and obesity than Europeans, the Asian population has a higher prevalence of diabetes than the European population (Chan et al., 2009). Given the differences across the ethnic group, there is a need to better understand what the factors underlying these interethnic differences are (Chan et al., 2009). Genetic epidemiological study has presented a difference in the risk allele frequency across ethnic groups. For example, a variant in *PEPD*, rs3786897, was only significant in East Asians. The risk allele frequency of the *TCF7L2* variant rs7903146 was lower in East Asians (5%) compared to those in Europeans (30%) (Diabetes Genetics Replication and Meta-analysis Consortium, Asian Genetic Epidemiology Network Type 2 Diabetes Consortium, South Asian Type 2 Diabetes Consortium, Mexican American Type 2 Diabetes Consortium, & Type 2 Diabetes Genetic Exploration by Nex-generation sequencing in muylti-Ethnic Samples Consortium, 2014).

3. Association between coffee consumption and risk of type 2 diabetes

Coffee is one of the most consumed beverages worldwide. Korea ranked 6th worldwide to import the highest amount of coffee. The average coffee consumption increased 1.08 cups/day in 2018 from 0.59 cups/day in 2001 (Figure 2) (Ministry of Health and Welfare Korea Centers for Disease Control and Prevention, 2020). The average frequency of coffee consumption among Koreans increased from 9 times/week in 2008 to 11 times/week in 2016, making coffee the most frequently consumed food (Ministry of Health and Welfare Korea Centers for Disease Control and Prevention, 2018). There could be large potential effects of coffee on the risk of diabetes because of its widespread consumption.

Coffee consumption has drawn attention in relation to type 2 diabetes prevention because of its widespread consumption and the effects of polyphenol compounds. Coffee consumption was inversely associated with the risk of type 2 diabetes in many meta-analyses of prospective studies (Ding, Bhupathiraju, Chen, van Dam, & Hu, 2014; Jiang, Zhang, & Jiang, 2014; van Dam & Hu, 2005). In a recent dose–response meta-analysis, the risk of type 2 diabetes decreased by 6% (RR:0.94; 95%CI: 0.93–0.95) for each cup/day increase of coffee consumption (Carlström & Larsson, 2018).

4. Mechanisms underlying the protective effects of coffee consumption on type 2 diabetes

Several mechanisms have been proposed regarding protective effects of coffee consumption on type 2 diabetes. Glucose regulation is an important function in the development of diabetes (American Diabetes Association, 2020). Coffee is a complex mixture of chemical compounds such as caffeine, cafestol, kahweol, and chlorogenic acids (Bidel et al., 2008; Costabile, Sarnsamak, & Hauge-Evans, 2018; van Dam, 2006). Of these, chlorogenic acids may have the potential to influence the glucose metabolism in peripheral, intestinal, and hepatic stage (Arion et al., 1997; Meng, Cao, Feng, Peng, & Hu, 2013; Peng et al., 2015). A number of studies have suggested that coffee consumption decreased in insulin resistance and increased in insulin sensitivity in peripheral tissues (Peng, Zhu, Zhong, Xu, & Wang, 2015). Chlorogenic acids stimulate glucose transporter 4 (GLUT4) which in turn prompt glucose uptake and insulin sensitivity (Peng, Zhu, Zhong, Xu, & Wang, 2015).

At the intestinal stage, chlorogenic acids inhibit the activities α-amylase and α-glucosidase (Meng et al., 2013). This action may reduce the postprandial blood glucose concentration which may be attributed to an improved sensitivity to insulin (Meng et al., 2013). Chlorogenic acids also stimulate the secretion of glucagon-like peptide-1 from gastrointestinal cells, thus it can stimulate insulin secretion (Johnston, Clifford, & Morgan, 2003).

At the hepatic stage, chlorogenic acids promote the uptake of glucose by liver cells

and regulates the overproduction of glucose by inhibiting glucose-6-phosphatase with the related effects of hepatic gluconeogenesis (Arion et al., 1997).

In addition to how compounds of coffee affect insulin secretion, potential protective effects on the pancreatic islet through antioxidant and anti-inflammatory effects are associated with protective effects of coffee consumption on type 2 diabetes (Natella & Scaccini, 2012; van Dam, 2006). Caffeine, chlorogenic acids, lignans, and melanoidins could act as antagonizing oxidative stress (Bloomer, Trepanowski, & Farney, 2013; Koloverou et al., 2015; Natella, Nardini, Giannetti, Dattilo, & Scaccini, 2002). Trigonelline also has been reported to act as antioxidant properties in pancreatic tissue (Zhou, Zhou, & Zeng, 2013). Several components of coffee have been shown anti-inflammatory effects, such as caffeine, chlorogenic acids, cafestrol, trigonelline, and kahweol (Zhou, Zhou, & Zeng, 2013). Epidemiological studies have shown that coffee consumption may reduce the levels of pro-inflammatory biomarkers, such as interleukin(IL)-1b, IL-4, IL-6, IL-10, and C-reactive proteins that can contribute to a reduced risk of type 2 diabetes (Imatoh et al., 2011; Natella & Scaccini, 2012; Williams et al., 2008).

III. Subjects and Methods

1. Study population

The participants were drawn from the four prospective cohorts of the Korean Genome and Epidemiology study (KoGES): the Health Examinees (HEXA) study, the Cardiovascular Disease Association Study (CAVAS), the Korea Association Resource (KARE) study, and the Healthy Twin (TWIN) study. The HEXA, CAVAS, and KARE studies consisted of community-dwellers and participants recruited from the national health examinee registry, aged 40 years or older at baseline. TWIN study consists of same-sex twins aged 30 years or older at baseline and their first-degree adult family members. The participants were recruited between 2004 and 2013 for the HEXA study, between 2005 and 2011 for the CAVAS, between 2001 and 2002 for the KARE study, and 2005 and 2013 for the TWIN study.

Follow-up examinations were conducted once from 2012 to 2016 for the HEXA study and from 2007 to 2017 for CAVAS (median follow-up: 4.25 years, 2.08 years, respectively). For the KARE study, a total of six follow-ups were conducted between 2003 and 2016 at 2 year intervals (median follow-up: 11.67 years). For the TWIN study, a total of three follow-ups were conducted from 2008 to 2015 (median follow-up: 3.17 years). Blood samples were drawn at baseline and at each follow-up. Blood samples were collected in a serum separator tube and two ethylenediaminetetraacetic acid (EDTA) tubes (Kim, Han, & Ko, 2017). Further information on the study design can be found elsewhere (Kim, Han, & Ko, 2017). For the HEXA study and the

CAVAS, participants who completed the follow-up were included, and for the KARE and the TWIN studies, anyone who participated in at least one follow-up was included.

For our analysis, there were a total of 214,911 participants at baseline, and participants with the following characteristics were excluded: had a history of type 2 diabetes, myocardial infarction, stroke, or cancer at baseline (n=40,386) (n=25,799 for the HEXA study; n=5,024 for the CAVAS; n=9,196 for the KARE study; and n=367 for the TWIN study); did not provide food-frequency questionnaires (FFQs) at baseline (n=3,712) (n=3,066 for the HEXA study; n=177 for the CAVAS; n=326 for the KARE study; and n=143 for the TWIN study); did not complete the survey of coffee consumption at baseline (n=2,318) (n=1,905 for the HEXA study; n=144 for the CAVAS; n=246 for the KARE study; and n=23 for the TWIN study); had implausible total energy intake at baseline (±3 standard deviations (SDs) from the mean of the log transformed total energy intake) (n=5,947) (n=4,883 for the HEXA study; n=474 for the CAVAS; n=412 for the KARE study; and n=178 for the TWIN study); did not provide blood samples at follow-up (n=134,027) (n=107,725 for the HEXA study; n=15,873 for the CAVAS; n=9,257 for the KARE study; and n=1,172 for the TWIN study); and had none of the follow-up information on fasting plasma glucose, HbA1c measurements, self-reported diagnosis of diabetes, and use of diabetes medication (n=2,690) (n=6 for the HEXA study; n=3 for the CAVAS; n=2,681 for the KARE study; and n=0 for the TWIN study) were further excluded. A total of 71,527 participants (n=54,122 for the HEXA study; n=9,994 for the

CAVAS; n=5,698 for the KARE study; and n=1,713 for the TWIN study) were included in this analysis. For the subgroup analysis, we further excluded participants who did not have genetic information (n=53,234 for the HEXA study; n=7,356 for the CAVAS; n=622 for the KARE study; and n=718 for the TWIN study). Therefore, among 71,527 participants, the DNA samples from a total of 9,597 participants were genotyped (n=888 for the HEXA study; n=2,638 for the CAVAS; n=5,076 for the KARE study; and n=995 for the TWIN study). Written informed consent was obtained from all study participants. The study protocol was approved by the Institutional Review Board of Seoul National University (IRB no. E1903/002-002).

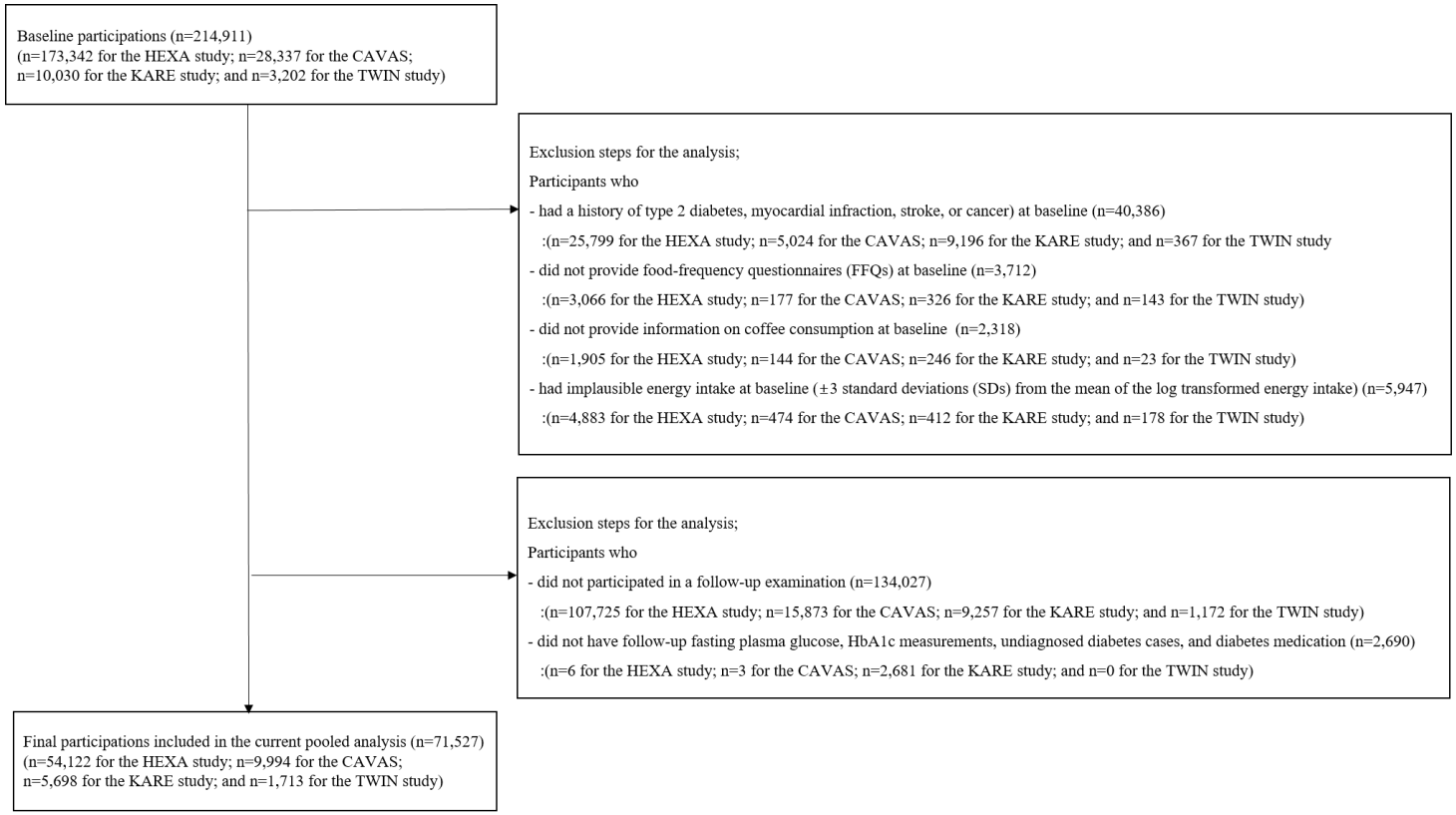

Figure 1. Flow diagram of study population included in the analysis

2. Ascertainment of type 2 diabetes

The concentrations of fasting plasma glucose and the 2 h plasma glucose level of the oral glucose tolerance test (OGTT) were measured by the hexokinase method (ADVIA 1650; Bayer, Inc.). In accordance with the type 2 diabetes criteria of the American Diabetes Association, confirmation of type 2 diabetes was defined as the presence of any one of the following (American Diabetes Association, 2020): 1) fasting plasma glucose level ≥126 mg/dL, 2) HbA1c level ≥6.5% 3) history of diagnosed diabetes, or 4) current use of hypoglycemic medication. Since only the KARE study participants measured the OGTT, an OGTT level ≥200 mg/dL was considered the confirmation of the type 2 diabetes. Incident cases were those who did not have diabetes at baseline and met any of the aforementioned conditions during follow-up, whichever occurred first.

3. Assessment of coffee and other factors

Coffee and green tea consumption was assessed using a 106-item semi-quantitative FFQ in the HEXA, CAVAS, and TWIN studies, and a 103-item semi-quantitative FFQ in the KARE study. The validity and reproducibility of the FFQs have been described in detail elsewhere (Ahn et al., 2007; Kim et al., 2003). Participants were asked to select from nine categories of coffee consumption frequency over the preceding year, ranging from almost never to 5 or more times per day in the HEXA, CAVAS, and TWIN studies and ranging from almost never to 3 or more times per day in the KARE study. The frequency of the coffee additives such as cream and

sugar was also collected. The portion size was composed of three categories (a half of, equal to, and 2 times of a standard serving size for HEXA, CAVAS, KARE, and TWIN studies). To estimate the pooled odds ratios (ORs) of the four prospective cohort studies, the categories of coffee consumption were unified into four categories: 0 to <0.5, 0.5 to <1, 1 to <3, and ≥3 cups per day. Green tea consumption was also assessed using the FFQs in the same way that coffee consumption was calculated.

Trained interviewers obtained information on the following demographic and lifestyle factors: education level; smoking status (never, past, and current smoker), the number of years spent smoking, and the number of cigarettes smoked daily; and alcohol drinking status (never, past, and current drinker), frequency of alcohol drinking, and serving size of alcohol across the studies. Physical activity was also assessed (none and frequency 1-2, 3-4, 5-6, and every day per week for the HEXA, CAVAS, TWIN studies). For the KARE study, the frequency and duration of types of physical activity (aerobics, jogging, swimming, tennis, golf, bowling, walking, and climbing) were assessed.

Pack-years of smoking were calculated by dividing the daily number of cigarettes by 20 and multiplying this result by the number of years smoked. Total alcohol consumption is calculated as grams of ethanol per day (Korea Health Promotion Institute, 2013). Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Metabolic equivalent hours (MET-h)/week was determined by multiplying the hours per week spent in each activity by the metabolic cost of each activity in METs (Korean Centers for Disease Control and

Prevention, 2017).

4. Genotyping and SNP selection

The genomic DNA samples isolated from the peripheral blood of the study participants in the HEXA and TWIN studies were directly genotyped with the Affymetrix Genome-Wide Human SNP array 6.0 (Kim et al., 2011). Individual genotypes were called with the birdseed genotyping algorithm (Kim et al., 2011). Some of the CAVAS participants were genotyped by the aforementioned method and the rest of the CAVAS participants were genotyped using Illumina Omni 1 Quad bead microarrays, isolated from peripheral blood drawn from the CAVAS participants (Kim et al., 2011; Kim et al., 2013). Participants in the KARE study were genotyped with the Affymetrix Genome-Wide Human SNP Array 5.0 (Cho et al., 2009). The individual genotypes were called by applying the Bayesian Robust Linear Model using the Mahalanobis Distance Genotyping Algorithm in the KARE study (Cho et al., 2009). The non-typed or missing genotypes for each participant in the KARE study were imputed using IMPUTE v246 with 1000 Genomes data (Moon et al., 2019). Genotyping with Affymetrix 5.0, Affymetrix 6.0, and Illumina Omni 1 M and quality control procedures have been described in detail previously (Cho et al., 2009; Kim et al., 2011; Kim et al., 2013).

In our study, 5 single nucleotide polymorphisms (SNPs) related to type 2 diabetes (*CDKAL1* rs7756992, *CDKN2A/B* rs10811661, *KCNJ11* rs5215, *KCNQ1* rs163184, and *PEPD* rs3786897) with suggestive significance ($P < 1 \times 10^{-6}$) among East Asian

populations was extracted based on evidence from a trans-ethnic meta-analysis (Diabetes Genetics Replication and Meta-analysis Consortium, Asian Genetic Epidemiology Network Type 2 Diabetes Consortium, South Asian Type 2 Diabetes Consortium, Mexican American Type 2 Diabetes Consortium, & Type 2 Diabetes Genetic Exploration by Nex-generation sequencing in muylti-Ethnic Samples Consortium, 2014). Four of the aforementioned 5 SNPs (*CDKAL1* rs7756992, *CDKN2A/B* rs10811661, *KCNJ11* rs5215, *KCNQ1* rs163184) were all available from direct genotyping within the HEXA, CAVAS, KARE and TWIN studies. Information on the remaining SNP (*PEPD* rs3786897) was only available within the CAVAS and KARE studies.

Table 1. Type 2 diabetes related genetic polymorphisms from previous studies

Locus	Lead SNP	Chr	Alleles		European 12,171 cases and 56,862 controls			East Asian 6,952 cases and 11,865 controls		
			Risk	Other	RAF	OR (95% CI)	*p*-value	RAF	OR (95% CI)	*p*-value
CDKAL1	rs7756992	6	G	A	0.26	1.2(1.16-1.25)	1.10E-21	0.60	1.14(1.09-1.20)	4.80E-08
KCNQ1	rs163184	11	G	T	0.50	1.09(1.04-1.13)	4.30E-05	0.39	1.16(1.10-1.23)	1.60E-08
KCNJ11	rs5215	11	C	T	0.38	1.08(1.04-1.12)	1.10E-05	0.35	1.14(1.09-1.20)	1.60E-07
CDKN2A/B	rs10811661	9	T	C	0.82	1.18(1.13-1.24)	1.20E-12	0.67	1.25(1.17-1.32)	6.30E-13
PEPD	rs3786897	19	A	G	0.57	1.02(0.98-1.06)	3.30E-01	0.40	1.17(1.10-1.24)	3.50E-07

Abbreviations: SNP, single nucleotide polymorphisms; Chr, chromosome; RAF, risk allele frequency; ORs, odds ratios; CIs, confidence intervals

(Diabetes Genetics Replication and Meta-analysis Consortium, Asian Genetic Epidemiology Network Type 2 Diabetes Consortium, South Asian Type 2 Diabetes Consortium, Mexican American Type 2 Diabetes Consortium, & Type 2 Diabetes Genetic Exploration by Nex-generation sequencing in muylti-Ethnic Samples Consortium, 2014)

5. Statistical analysis

Multivariate logistic regression models were used to examine the associations between coffee consumption and the risk of type 2 diabetes. Logistic regression to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) were used because participants who provided blood samples at both follow-up and baseline and ascertained type 2 diabetes by fasting plasma glucose level ≥126 mg/dL, HbA1c level 6.5%, or OGTT level ≥200 mg/Dl were included. ORs and 95% CIs according to the categories of coffee consumption and per cup increment were estimated.

In multivariable analyses, age (years, continuous), sex, BMI (<18.5, 18.5 to <23, 23 to <25, and ≥25 kg/m^2), alcohol intake (never, ethanol g/day <10, 10-<20, 20-<30, 30-<40, 40-<50, 50-<60, ≥60 for men and never, ethanol g/d <10, 10<20, ≥20 for women for HEXA and KARE, never, ethanol g/day <10, 10-<20, 20-<30, 30-<40, ≥40 for men and never, ethanol g/d <10, ≥10 for women for CAVAS, and never, ethanol g/day <10, ≥10 for men and never, ever for women for TWIN), smoking status (never, pack-years <10, 10-<20, 20-<30, ≥30 for men and never, pack-years <5, 5-<10, ≥10 for women for HEXA, never, pack-years <10, 10-<20, 20-<30, ≥30 for men and never, pack-years <5, ≥5 for women for CAVAS, never, pack-years <10, 10-<20, 20-<30, 30-<40 ≥40 for men and never, pack-years <5, 5-<10, ≥10 for women for KARE, never/ever for men and never/ever for women for TWIN), regular exercise (none, physical activity frequency 1-2, 3-4, 5-6, and every day per week in HEXA, CAVAS, TWIN, and tertile in MET-h/week in KARE), education level (elementary school or less, middle school, and high school or above), green tea

intake (0 to <1, 1 to <2, and ≥2 cups/day), and total energy intake (kcal/day, continuous) were adjusted. Because adjustment for fruit and vegetable intake, meat intake, and dairy intake did not change our estimates appreciably, these variables were not included in our final model.

To test for linear trends across categories of coffee consumption, the median of each category of coffee consumption as a continuous variable was modeled. The pooled ORs were estimated using random effects model when there was evidence of heterogeneity or a fixed effect model when there was no heterogeneity (Cochran, 1954). Heterogeneity across the studies using Q statistics was tested (Cochran, 1954). Subgroup analyses was performed to examine whether the associations between coffee consumption and type 2 diabetes varied by age (age <50 or ≥50 years), sex, BMI (<25 or ≥25 kg/m^2), smoking status (never smoker or ever smoker), alcohol drinking (non-drinker or current drinker), and type 2 diabetes susceptibility genes using a meta-regression model (Thompson & Higgins, 2002). Test for non-linearity of the association was performed using restricted cubic splines (Orsini, Li, Wolk, Khudyakov, & Spiegelman, 2012). For the cubic spline analysis, all studies were combined into a single dataset and then adjusted covariates. Top 1% of participants in the aggregated dataset were excluded in the cubic spline analysis to reduce excessive influence of extreme coffee consumption. All statistical tests were two-sided, and P values less than 0.05 were considered statistically significant. All analyses were performed using SAS software, version 9.4 (SAS Institute Inc, Cary, North Carolina) and STATA SE 15 (Stata Corporation) for the meta regression.

IV. Results

1. General characteristics of study participants

A total of 4,600 incident type 2 diabetes cases were identified among participants during median follow-up periods of up to 2-13 years across the 4 studies. The general characteristics of the HEXA, CAVAS, KARE and TWIN study according to the consumption of coffee are reported in Table 2- Table 5.

In the HEXA study, the mean (SD) values for the age, BMI, pack-years of smoking, and ethanol g/day of those who drank ≥3cups/day of coffee of was 51.12 (7.70) years, 24.04 (2.86) kg/m^2, 9.33 (15.35) pack-years, and 9.19 (21.81) g/day, respectively. In the CAVAS, the mean (SD) values for the age, BMI, pack-years, and ethanol g/day of those who drank ≥3cups/day of coffee of was 58.50 (9.27) years, 24.50 (3.09) kg/m^2, 14.17 (21.63) pack-years, and 10.26 (23.08) g/day, respectively. In the KARE study, the mean (SD) values for the age, BMI, pack-years, and ethanol g/day of the participants was 48.60 (7.48) years, 24.72 (3.08) kg/m^2, 17.35 (19.62) pack-years, and 24.72 (3.08) g/day, respectively. In the TWIN study, the mean (SD) values for the age, BMI, pack-years, and ethanol g/day of the participants was 41.73 (10.12) years, 23.88 (3.19) kg/m^2, 9.55 (16.96) pack-years, and 16.36 (53.90) g/day, respectively. Overall, participants with higher coffee consumption were younger, had higher levels of smoking and alcohol drinking, and had higher education levels. Coffee drinkers were more likely to have higher energy intake and consume green tea than were non-drinkers.

Table 2. Baseline characteristic of participants from the HEXA study according to coffee consumption

	Coffee consumption (cups/day)			
	0 to <0.5	**0.5 to <1**	**1 to <3**	**≥3**
HEXA				
Total population no.	15,480	5,310	22,598	10,734
Age at baseline (years of age)	54.51±7.82	52.73±7.86	52.89±7.87	51.12±7.70
Sex				
Men	3,980 (25.71)	1,692 (31.86)	6,883 (30.46)	4,981 (46.40)
Women	11,500 (74.29)	3,618 (68.14)	15,715 (69.54)	5,753 (53.60)
BMI (kg/m^2)	23.42±2.75	23.74±2.75	23.85±2.79	24.04±2.86
Cigarette smoking (pack-years) [1)]	2.79±8.57	4.13±10.41	4.47±10.84	9.33±15.35
Alcohol drinking (g/day) [1)]	4.98±26.92	6.00±16.80	6.03±15.20	9.19±21.81
Regular exercise [1)]				
No	6,572 (42.61)	2,151 (40.59)	10,069 (44.72)	5,279 (49.30)
Yes	8,852 (57.39)	3,148 (59.41)	12,447 (55.28)	5,428 (50.70)
Education level [1)]				
Elementaty school or less	2,778 (18.20)	643 (12.22)	2,996 (13.42)	1,026 (9.65)
Middle school	2,828 (18.53)	754 (14.33)	3,462 (15.51)	1,443 (13.57)
High school or above	9,655 (63.27)	3,863 (73.44)	15,866 (71.07)	8,163 (76.78)
Total energy intake (kcal/day)	1,649.55±493.61	1,697.68±494.80	1,780.62±490.32	1,881.3±541.84
Green tea drinking (cups/day)	0.34±0.77	0.40±0.75	0.45±0.80	0.50±0.99

Abbreviations: HEXA, The Health Examinees Study; BMI, body mass index

1)The total number of participants was different in the study (n=54,122 for the HEXA study) because of missing values

Continuous variables are reported as mean±standard deviation(SD) and categorical variables are reported as No. (%)

Table 3. Baseline characteristic of participants from the CAVAS according to coffee consumption

	Coffee consumption (cups/day)			
	0 to <0.5	**0.5 to <1**	**1 to <3**	**≥3**
CAVAS				
Total population no.	3,375	889	3,991	1,739
Age at baseline (years of age)	61.84±9.07	59.79±9.25	60.50±9.09	58.50±9.27
Sex				
Men	1,038 (30.76)	354 (39.82)	1,451 (36.36)	937 (53.88)
Women	2,337 (69.24)	535 (60.18)	2,540 (63.64)	802 (46.12)
BMI (kg/m^2)	24.08±3.05	24.52±3.13	24.53±3.06	24.50±3.09
Cigarette smoking (pack-years) [1)]	4.75±13.26	6.99±15.64	7.15±15.96	14.17±21.63
Alcohol drinking (g/day) [1)]	7.01±22.73	10.69±25.78	8.40±22.47	10.26±23.08
Regular exercise [1)]				
No	2,303 (68.34)	580 (65.24)	2,756 (69.11)	1,174 (67.55)
Yes	1,067 (31.66)	309 (34.76)	1,232 (30.89)	564 (32.45)
Education level [1)]				
Elementaty school or less	2,085 (61.98)	433 (48.82)	2,165 (54.30)	754 (43.43)
Middle school	532 (15.81)	150 (16.91)	713 (17.88)	345 (19.87)
High school or above	747 (22.21)	304 (34.27)	1,109 (27.82)	637 (36.69)
Total energy intake (kcal/day)	1,541.67±474.21	1,634.86±492.65	1,679.10±469.95	1,846.12±545.15
Green tea drinking (cups/day)	0.33±0.89	0.29±0.65	0.40±0.82	0.48±1.00

Abbreviations: CAVAS, Cardiovascular Disease Association Study; BMI, Body Mass Index

1)The total number of participants was different in the study (n=9,994 for the CAVAS) because of missing values

Continuous variables are reported as mean±standard deviation(SD) and categorical variables are reported as No. (%)

Table 4. Baseline characteristic of participants from the KARE study according to coffee consumption

	Coffee consumption (cups/day)			
	0 to <0.5	**0.5 to <1**	**1 to <3**	**≥3**
KARE				
Total population no.	2,079	546	2,280	793
Age at baseline (years of age)	53.41±8.70	50.71±8.16	50.20±8.14	48.60±7.48
Sex				
Men	804 (38.67)	280 (51.28)	1,027 (45.04)	551 (69.48)
Women	1,275 (61.33)	266 (48.72)	1,253 (54.96)	242 (30.52)
BMI (kg/m^2)	24.26±3.10	24.70±2.89	24.60±2.99	24.72±3.08
Cigarette smoking (pack-years) [1)]	5.61±12.29	8.19±13.33	8.37±14.72	17.35±19.62
Alcohol drinking (g/day) [1)]	6.86±17.69	9.64±19.92	9.35±21.12	13.22±25.44
Exercise (MET-h/wk) [1)]	1,596.83±970.33	1,574.97±985.81	1,507.31±911.05	1,441.54±961.17
Education level [1)]				
Elementaty school or less	1,315 (63.68)	274 (50.46)	1,108 (48.85)	305 (38.56)
Middle school	538 (26.05)	182 (33.52)	810 (35.71)	329 (41.59)
High school or above	212 (10.27)	87 (16.02)	350 (15.43)	157 (19.85)
Total energy intake (kcal/day)	1,861.91±614.64	1,933.38±609.98	1,971.82±589.86	2,115.02±647.64
Green tea drinking (cups/day)	0.26±0.59	0.29±0.47	0.35±0.65	0.36±0.72

Abbreviations: KARE, the Korea Association Resource; BMI, Body Mass Index; MET-h/wk; Metabolic Equivalent hours.
1)The total number of participants was different in the study (n=5,698 for the KARE study) because of missing values
Continuous variables are reported as mean±standard deviation(SD) and categorical variables are reported as No. (%)

Table 5. Baseline characteristic of participants from the TWIN study according to coffee consumption

	Coffee consumption (cups/day)			
	0 to <0.5	**0.5 to <1**	**1 to <3**	**≥3**
TWIN				
Total population no.	478	252	590	393
Age at baseline (years of age)	43.21±14.66	43.99±13.78	42.58±11.60	41.73±10.12
Sex				
Men	161 (33.68)	86 (34.13)	209 (35.42)	194 (49.36)
Women	317 (66.32)	166 (65.87)	381 (64.58)	199 (50.64)
BMI (kg/m^2)	23.31±3.43	23.68±3.36	23.62±3.10	23.88±3.19
Cigarette smoking (pack-years) [1)]	2.54±7.75	3.22±8.24	4.37±9.57	9.55±16.96
Alcohol drinking (g/day) [1)]	7.09±16.94	7.36±14.26	8.94±18.36	16.36±53.90
Regular exercise [1)]				
No	291 (62.58)	161 (65.18)	384 (66.67)	270 (70.13)
Yes	174 (37.42)	86 (34.82)	192 (33.33)	115 (29.87)
Education level [1)]				
Elementaty school or less	75 (15.82)	30 (11.95)	64 (10.87)	38 (9.69)
Middle school	28 (5.91)	24 (9.56)	38 (6.45)	28 (7.14)
High school or above	371 (78.27)	197 (78.49)	487 (82.68)	326 (83.16)
Total energy intake (kcal/day)	1,815.86±707.23	1,869.54±647.56	1,904.06±632.84	2,069.78±697.32
Green tea drinking (cups/day)	1.52±4.00	1.33±2.36	1.85±3.47	2.36±4.27

Abbreviations: TWIN, the Healthy Twin study; BMI, Body Mass Index

1)The total number of participants was different in the study (n=1,713 for the TWIN study) because of missing values

Continuous variables are reported as mean±standard deviation(SD) and categorical variables are reported as No. (%)

2. Association between coffee consumption and the risk of type 2 diabetes

Median follow up of the HEXA, CAVAS, KARE, and the TWIN study was 4.25, 2.08, 11.67, 3.17 years, respectively. Table 6 shows the ORs and 95% CIs of type 2 diabetes incidence according to the coffee consumption. An inverse association between coffee consumption and risk of type 2 diabetes was found. Compared to 0 to <0.5 cups/day of coffee consumption, pooled ORs (95% CIs) were 1.02 (0.91-1.14) for 0.5 to <1 cups/day of coffee consumption, 0.97 (0.90-1.05) for 1 to <3 cups/day of coffee consumption, 0.89 (0.80-0.98) for ≥3 cups/day of coffee consumption (*p* for trend=0.01) (Table 2). There was an inverse association in each cohort; compared 0 to <0.5 cups/day of coffee consumption, ORs (95%CIs) with ≥3 cups/day of coffee consumption were 0.90 (0.80-1.01; *p* for trend=0.04) in the HEXA study, 0.84 (0.57-1.24; *p* for trend=0.38) in the CAVAS study, 0.88 (0.71-1.09; *p* for trend=0.29) in the KARE study, and 0.82 (0.33-1.06; *p* for trend=0.65) in the TWIN study. Increment in 1 cup/day of coffee consumption was associated with a marginally significant 3% lower the risk of type 2 diabetes (pooled OR=0.97 [95% CI=0.95-1.00]). In a restricted cubic spline analysis, coffee consumption was nonlinearly associated with a lower risk of type 2 diabetes (*p* for curvature=0.0001, Figure 4). A decrease in the risk of type 2 diabetes was observed when 0.6 cups/day to 3 cups/day of coffee was consumed, but we did not observe any apparent further decrease in the risk of type 2 diabetes above ≥3 cups/day.

Table 6. Odds ratios (ORs) and 95% confidence intervals (CIs) for the risk of type 2 diabetes according to coffee consumption

	median follow-up period (years)	Coffee consumption (cups/day)				*p* for trend	per 1 cup/day increment
		0 to <0.5	0.5 to <1	1 to <3	≥3		
HEXA	4.25						
Case/Total no.		810/15,480	299/5,310	1,199/22,598	561/10,734		
Age-sex adjusted OR (CIs)		1.00 (reference)	1.12 (0.97-1.28)	1.05 (0.96-1.15)	1.03 (0.92-1.15)	0.94	1.02 (0.99-1.04)
MV adjusted OR (CIs)		1.00 (reference)	1.05 (0.92-1.21)	0.97 (0.88-1.06)	0.90 (0.80-1.01)	0.04	0.98 (0.96-1.01)
CAVAS	2.08						
Case/Total no.		92/3,375	28/889	121/3,991	43/1,739		
Age-sex adjusted OR (CIs)		1.00 (reference)	1.17 (0.76-1.80)	1.12 (0.85-1.48)	0.90 (0.62-1.31)	0.62	0.96 (0.88-1.06)
MV adjusted OR (CIs)		1.00 (reference)	1.11 (0.72-1.71)	1.05 (0.79-1.39)	0.84 (0.57-1.24)	0.38	0.94 (0.85-1.04)
KARE	11.67						
Case/Total no.		515/1,564	126/420	556/1,724	192/601		
Age-sex adjusted OR (CIs)		1.00 (reference)	0.95 (0.76-1.19)	1.06 (0.92-1.22)	1.02 (0.84-1.25)	0.71	0.98 (0.93-1.03)
MV adjusted OR (CIs)		1.00 (reference)	0.90 (0.72-1.14)	0.99 (0.85-1.15)	0.88 (0.71-1.09)	0.29	0.95 (0.90-1.00)
TWIN	3.17						
Case/Total no.		18/478	10/252	17/590	13/393		
Age-sex adjusted OR (CIs)		1.00 (reference)	1.04 (0.44-1.46)	0.86 (0.43-1.68)	1.08 (0.48-1.40)	0.90	1.10 (0.92-1.31)
MV adjusted OR (CIs)		1.00 (reference)	1.00 (0.42-1.39)	0.75 (0.38-1.48)	0.82 (0.33-1.06)	0.65	0.94 (0.90-1.00)

Table 6. Odds ratios (ORs) and 95% confidence intervals (CIs) for the risk of type 2 diabetes according to coffee consumption (*Continued*)

	median follow-up period (years)	coffee consumption (cups/day)				*p* for trend	per 1 cup/day increment
		0 to <0.5	0.5 to <1	1 to <3	≥3		
Pooled							
MV adjusted OR (CIs)		1.00 (reference)	1.02 (0.91-1.14)	0.98 (0.90-1.05)	0.89 (0.81-0.98)	0.01	0.97 (0.95-1.00)

Abbreviations: MV, Multivariate; ORs, Odds Ratios; CIs, confidence intervals; HEXA, Health Examinee; CAVAS, Cardiovascular Disease Association Study; KARE, the Korea Association Resource; TWIN, the Healthy Twin study

MV adjusted: age (years, continuous), sex (men, women), BMI (<18.5, 18.5- <23, 23-<25, and ≥25 kg/m^2), alcohol intake (never, ethanol g/day <10, 10-<20, 20-<30, 30-<40, 40-<50, 50-<60, ≥60 for men; never, ethanol g/d <10, 10<20, ≥20 for women for HEXA and KARE, never, ethanol g/day <10, 10-<20, 20-<30, 30-<40, ≥40 for men; never, ethanol g/d <10, ≥10 for women for CAVAS, and never, ethanol g/day <10, ≥10 for men; never, ever for women for TWIN), smoking status (never, pack-years <10, 10-<20, 20-<30, ≥30 for men; never, pack-years <5, 5-<10, ≥10 for women for HEXA, never, pack-years <10, 10-<20, 20-<30, ≥30 for men; never, pack-years <5, ≥5 for women for CAVAS, never, pack-years <10, 10-<20, 20-<30, 30-<40 ≥40 for men; never, pack-years <5, 5-<10, ≥10 for women for KARE, never/ever for men and never/ever for women for TWIN), regular exercise (no, physical activity frequency 1-2, 3-4, 5-6, and every day per week for HEXA, CAVAS, TWIN, and tertile in MET-h/wk for KARE), education level (elementary school or less, middle school, and high school or above), green tea intake (0-<1, 1-<2, and ≥2 cups/day), and total energy intake (kcal/day, continuous)

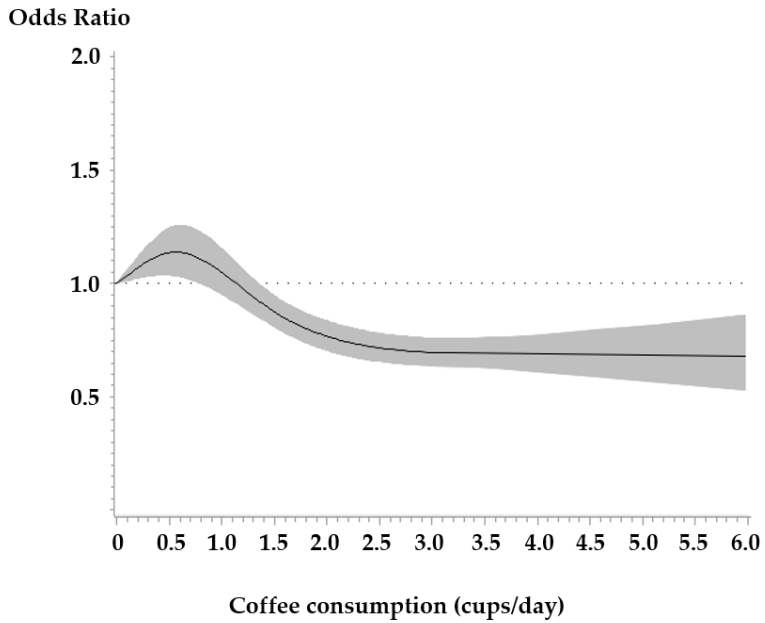

Figure 2. Continuous dose-response association between coffee consumption and the risk of type2 diabetes with restricted cubic splines

The solid line represents the estimated Odds ratios (ORs), and the shaded area represents 95% confidence intervals (CIs).
p for curvature=0.0001

3. Subgroup analyses on the association between coffee consumption and type 2 diabetes

3.1. Subgroup analysis on the association between coffee consumption and type 2 diabetes stratified by type 2 diabetes susceptibility genes

Whether the association between coffee consumption and the risk of type 2 diabetes was modified by type 2 diabetes susceptibility genes was examined. Table 7 shows ORs and 95% CIs for the risk of type 2 diabetes according to coffee consumption stratified by type 2 diabetes susceptibility genes in dominant model. The inverse association did not vary by polymorphisms of rs7756992 in *CDKAL1*, rs10811661 in *CDKN2A/B*, rs5215 in *KCNJ11*, rs163184 in *KCNQ1*, and rs3786897 in *PEPD* (*p* for interaction=0.56, 0.97, 0.73, 0.62, 0.68, respectively). There was an inverse association in each risk allele; compared 0 to <0.5 cups/day of coffee consumption, ORs (95%CIs) with ≥3 cups/day of coffee consumption were 0.83 (0.66-1.04) in the risk allele of rs7756992, 0.86 (0.68-1.06) in the risk allele of 10811661, 0.87 (0.68-1.12) in the risk allele of 5215, 0.81 (0.63-1.04) in the risk allele of 163184, 0.82 (0.65-1.04) in the risk allele of 3786897.

Table 8 presents the ORs and 95% CIs for the risk of type 2 diabetes according to coffee consumption stratified by type 2 diabetes susceptibility genes in recessive model. The inverse association did not vary by polymorphisms of rs7756992 in

CDKAL1, rs10811661 in *CDKN2A/B*, rs5215 in *KCNJ11*, rs163184 in *KCNQ1*, and rs3786897 in *PEPD* (p for interaction=0.18, 0.31, 0.60, 0.80, 0.80, respectively). There was an inverse association in each risk allele; compared 0 to <0.5 cups/day of coffee consumption, ORs (95%CIs) with ≥3 cups/day of coffee consumption were 0.99 (0.69-1.42 in the risk allele of 10811661, 0.85 (0.49-1.45) in the risk allele of 5215, 0.81 (0.50-1.33) in the risk allele of 163184, 0.89 (0.61-1.29) in the risk allele of 3786897.

Table 9 shows ORs and 95% CIs for the risk of type 2 diabetes according to coffee consumption stratified by type 2 diabetes susceptibility genes in additive model. The inverse association did not vary by polymorphisms of rs7756992 in *CDKAL1*, rs10811661 in *CDKN2A/B*, rs5215 in *KCNJ11*, rs163184 in *KCNQ1*, and rs3786897 in *PEPD* (*p* for interaction=0.66, 0.46, 0.73, 0.66, 0.52, respectively).

Table 7. Odds Ratios (ORs) and 95% confidence intervals (CIs) for the risk of type 2 diabetes according to coffee consumption stratified by type 2 diabetes-related SNPs: Dominant model

		coffee consumption (cups/day)				*p* for trend	per 1cup/day increment	*p* for interaction
SNP (Risk/Other)		**0 to <0.5**	**0.5 to <1**	**1 to <3**	**≥3**			
rs7756992(G/A)								0.56
GG+AG	Case no.	424	112	448	165			
	Pooled OR (CIs)	1.00 (reference)	0.92 (0.72- 1.17)	0.93 (0.79- 1.09)	0.83 (0.66- 1.04)	0.11	0.95 (0.89-1.00)	
AA	Case no.	111	21	117	38			
	Pooled OR (CIs)	1.00 (reference)	0.79 (0.45- 1.39)	1.03 (0.75- 1.42)	0.99 (0.61- 1.59)	0.87	0.95 (0.84-1.07)	
rs10811661(T/C)								0.97
TT+CT	Case no.	437	113	452	170			
	Pooled OR (CIs)	1.00 (reference)	0.97 (0.75- 1.23)	0.93 (0.79- 1.09)	0.85 (0.68- 1.06)	0.15	0.95 (0.89-1.00)	
CC	Case no.	97	20	113	34			
	Pooled OR (CIs)	1.00 (reference)	0.75 (0.44- 1.31)	1.03 (0.74- 1.43)	0.86 (0.52- 1.41)	0.69	0.97 (0.86-1.09)	
rs5215(C/T)								0.73
CC+CT	Case no.	347	77	371	131			
	Pooled OR (CIs)	1.00 (reference)	0.83 (0.62- 1.11)	0.98 (0.83- 1.17)	0.87 (0.68- 1.12)	0.34	0.96 (0.90-1.02)	
TT	Case no.	187	55	194	72			
	Pooled OR (CIs)	1.00 (reference)	1.08 (0.74- 1.56)	0.90 (0.71- 1.15)	0.80 (0.56- 1.13)	0.22	0.95 (0.87-1.03)	

Table 7. Odds Ratios (ORs) and 95% confidence intervals (CIs) for the risk of type 2 diabetes according to coffee consumption stratified by type 2 diabetes-related SNPs: Dominant model (*Continued*)

		coffee consumption (cups/day)				*p* for trend	per 1cup/day increment	*p* for interaction
SNP (Risk/Other)		**0 to <0.5**	**0.5 to <1**	**1 to <3**	**≥3**			
rs163184(G/T)								0.62
GG+TG	Case no.	381	85	399	133			
	Pooled OR (CIs)	1.00 (reference)	0.81 (0.62- 1.07)	0.99 (0.83- 1.17)	0.81 (0.63- 1.04)	0.15	0.94 (0.88-1.00)	
TT	Case no.	154	48	166	71			
	Pooled OR (CIs)	1.00 (reference)	1.10 (0.74- 1.63)	0.90 (0.69- 1.17)	0.94 (0.65- 1.35)	0.78	0.99 (0.91-1.08)	
rs3786897(A/G) *								0.68
	Case no.	403	98	440	149			
AA+GA	Pooled OR (CIs)	1.00 (reference)	0.88 (0.68-1.14)	0.95 (0.80-1.12)	0.82 (0.65-1.04)	0.81	1.04 (0.80-1.35)	
	Case no.	87	19	87	34			
GG	Pooled OR (CIs)	1.00 (reference)	0.94 (0.52-1.70)	1.15 (0.79-1.65)	1.31 (0.78-2.18)	0.27	1.01 (0.89-1.15)	

Abbreviations: ORs, Odds ratios; CIs, Confidence intervals; SNP, Single nucleotide polymorphisms

MV adjusted: age (years, continuous), sex (men, women), BMI (<23 and ≥23 kg/m^2), alcohol intake (never, ever for men; never, ever for women), smoking status (never, ever for HEXA, CAVAS, TWIN, never, pack-years <10, 10-<20, 20-<30, 30-<40 ≥40 for men; never, pack-years <5, 5-<10, ≥10 for women for KARE), education level (middle school or less, and high school or above), green tea intake (0-<2, and ≥2 cups/day), and total energy intake (kcal/day, continuous)

*Only the CAVAS and the KARE studies were included in analysis

Table 8. Odds Ratios (ORs) and 95% confidence intervals (CIs) for the risk of type 2 diabetes according to coffee consumption stratified by type 2 diabetes-related SNPs: Recessive model

		coffee consumption (cups/day)				*p* for trend	per 1cup/day increment	*p* for interaction
SNP (Risk/Other)		**0 to <0.5**	**0.5 to <1**	**1 to <3**	**≥3**			
rs7756992(G/A)								0.18
GG	Case no.	156	43	168	71			
	Pooled OR (CIs)	1.00 (reference)	1.16 (0.77-1.73)	1.00 (0.77-1.31)	1.04 (0.72-1.51)	0.79	1.02 (0.93-1.11)	
AA+AG	Case no.	379	90	397	132			
	Pooled OR (CIs)	1.00 (reference)	0.83 (0.63-1.09)	0.93 (0.78-1.10)	0.78 (0.61-1.00)	0.05	0.92 (0.87-0.98)	
rs10811661(T/C)								
TT	Case no.	171	49	171	73			0.31
	Pooled OR (CIs)	1.00 (reference)	1.12 (0.76-1.66)	0.87 (0.67-1.13)	0.99 (0.69-1.42)	0.96	0.96 (0.87-1.05)	
CC+CT	Case no.	363	84	394	131			
	Pooled OR (CIs)	1.00 (reference)	0.84 (0.64-1.11)	0.98 (0.83-1.17)	0.79 (0.62-1.02)	0.09	0.95 (0.89-1.01)	
rs5215(C/T)								
CC	Case no.	94	20	102	33			0.60
	Pooled OR (CIs)	1.00 (reference)	1.15 (0.62-2.11)	1.02 (0.71-1.47)	0.85 (0.49-1.45)	0.61	0.94 (0.82-1.09)	
TT+CT	Case no.	440	112	463	170			
	Pooled OR (CIs)	1.00 (reference)	0.90 (0.71-1.15)	0.95 (0.81-1.11)	0.86 (0.69-1.08)	0.21	0.95 (0.90-1.00)	

Table 8. Odds Ratios (ORs) and 95% confidence intervals (CIs) for the risk of type 2 diabetes according to coffee consumption stratified by type 2 diabetes-related SNPs: Recessive model (*Continued*)

SNP (Risk/Other)		Coffee consumption (cups/day)				*p* for trend	per 1cup/day increment	*p* for interaction
		0 to <0.5	0.5 to <1	1 to <3	≥3			
rs163184(G/T)								0.80
GG	Case no.	105	20	114	38			
	Pooled OR (CIs)	1.00 (reference)	0.76 (0.42-1.37)	1.09 (0.76-1.55)	0.81 (0.50-1.33)	0.55	0.92 (0.82-1.04)	
TT+TG	Case no.	430	113	451	166			
	Pooled OR (CIs)	1.00 (reference)	0.96 (0.75-1.22)	0.94 (0.81-1.10)	0.87 (0.70-1.09)	0.23	0.96 (0.91-1.02)	
rs3786897(A/G)*								
AA	Case no.	165	32	183	63			0.80
	Pooled OR (CIs)	1.00 (reference)	0.74 (0.48-1.16)	0.91 (0.70-1.18)	0.89 (0.61-1.29)	0.63	0.96 (0.87-1.06)	
GG+GA	Case no.	325	85	344	120			
	Pooled OR (CIs)	1.00 (reference)	1.02 (0.76-1.35)	1.04 (0.86-1.25)	0.92 (0.71-1.20)	0.64	1.05 (0.80-1.38)	

Abbreviations: ORs, Odds ratios; CIs, Confidence intervals; SNP, Single nucleotide polymorphisms

MV adjusted: age (years, continuous), sex (men, women), BMI (<23 and ≥23 kg/m^2), alcohol intake (never, ever for men; never, ever for women), smoking status (never, ever for HEXA, CAVAS, TWIN, never, pack-years <10, 10-<20, 20-<30, 30-<40 ≥40 for men; never, pack-years <5, 5-<10, ≥10 for women for KARE), education level (middle school or less, and high school or above), green tea intake (0-<2, and ≥2 cups/day), and total energy intake (kcal/day, continuous)

*Only the CAVAS and the KARE studies were included in analysis

Table 9. Odds Ratios (ORs) and 95% confidence intervals (CIs) for the risk of type 2 diabetes according to coffee consumption stratified by type 2 diabetes-related SNPs: Additive model

		coffee consumption (cups/day)				*p* for trend	per 1cup/day increment	*p* for interaction
SNP (Risk/Other)		**0 to <0.5**	**0.5 to <1**	**1 to <3**	**≥3**			
rs7756992(G/A)								0.66
GG	Case no.	156	43	168	71			
	Pooled OR (CIs)	1.00 (reference)	1.16 (0.77-1.73)	1.00 (0.77-1.31)	1.04 (0.72-1.51)	0.80	1.02 (0.93-1.11)	
AG	Case no.	268	69	280	94			
	Pooled OR (CIs)	1.00 (reference)	0.83 (0.61-1.14)	0.89 (0.72-1.09)	0.74 (0.55-0.99)	0.02	0.92 (0.85-0.99)	
AA	Case no.	111	21	117	38			
	Pooled OR (CIs)	1.00 (reference)	0.79 (0.45-1.38)	1.03 (0.75-1.42)	0.98 (0.61-1.59)	0.96	0.95 (0.84-1.07)	
rs10811661(T/C)								0.46
TT	Case no.	171	49	171	73			
	Pooled OR (CIs)	1.00 (reference)	1.12 (0.76-1.66)	0.87 (0.67-1.13)	0.99 (0.69-1.42)	0.96	0.96 (0.87-1.05)	
CT	Case no.	266	64	281	97			
	Pooled OR (CIs)	1.00 (reference)	0.90 (0.65-1.24)	0.96 (0.78-1.18)	0.75 (0.56-1.00)	0.11	0.93 (0.86-1.00)	
CC	Case no.	97	20	113	34			
	Pooled OR (CIs)	1.00 (reference)	0.75 (0.43-1.31)	1.03 (0.74-1.43)	0.86 (0.52-1.41)	0.50	0.97 (0.86-1.09)	

Table 9. Odds Ratios (ORs) and 95% confidence intervals (CIs) for the risk of type 2 diabetes according to coffee consumption stratified by type 2 diabetes-related SNPs: Additive model (*Continued*)

		coffee consumption (cups/day)				*p* for trend	per 1cup/day increment	*p* for interaction
SNP (Risk/Other)		**0 to <0.5**	**0.5 to <1**	**1 to <3**	**≥3**			
rs5215(C/T)								0.73
CC	Case no.	94	20	102	33			
	Pooled OR (CIs)	1.00 (reference)	1.15 (0.62-2.11)	1.02 (0.71-1.47)	0.86 (0.50-1.47)	0.49	0.94 (0.82-1.09)	
CT	Case no.	253	57	269	98			
	Pooled OR (CIs)	1.00 (reference)	0.79 (0.56-1.09)	0.99 (0.81-1.22)	0.88 (0.66-1.18)	0.55	0.95 (0.88-1.03)	
TT	Case no.	187	55	194	72			
	Pooled OR (CIs)	1.00 (reference)	1.07 (0.73-1.54)	0.90 (0.70-1.15)	0.79 (0.56-1.12)	0.08	0.94 (0.87-1.03)	
rs163184(G/T)								0.66
GG	Case no.	105	20	114	38			
	Pooled OR (CIs)	1.00 (reference)	0.76 (0.42-1.37)	1.09 (0.76-1.55)	0.81 (0.50-1.33)	0.55	0.92 (0.82-1.04)	
TG	Case no.	276	65	285	95			
	Pooled OR (CIs)	1.00 (reference)	0.85 (0.62-1.16)	0.98 (0.80-1.20)	0.83 (0.62-1.12)	0.55	0.94 (0.88-1.02)	
TT	Case no.	154	48	166	71			
	Pooled OR (CIs)	1.00 (reference)	1.10 (0.74-1.62)	0.89 (0.69-1.16)	0.92 (0.64-1.33)	0.52	0.99 (0.90-1.08)	

Table 9. Odds Ratios (ORs) and 95% confidence intervals (CIs) for the risk of type 2 diabetes according to coffee consumption stratified by type 2 diabetes-related SNPs: Additive model (*Continued*)

SNP (Risk/Other)		coffee consumption (cups/day) 0 to <0.5	0.5 to <1	1 to <3	≥3	*p* for trend	per 1cup/day increment	*p* for interaction
rs3786897(A/G)*								0.52
AA	Case no.	165	32	183	63			
	Pooled OR (CIs)	1.00 (reference)	0.74 (0.48-1.16)	0.91 (0.70-1.18)	0.89 (0.61-1.29)	0.63	0.96 (0.87-1.06)	
GA	Case no.	238	66	257	86			
	Pooled OR (CIs)	1.00 (reference)	1.01 (0.73-1.40)	0.98 (0.79-1.22)	0.79 (0.58-1.08)	0.26	1.07 (0.74-1.55)	
GG	Case no.	87	19	87	34			
	Pooled OR (CIs)	1.00 (reference)	0.94 (0.52-1.70)	1.15 (0.79-1.65)	1.31 (0.78-2.18)	0.27	1.01 (0.89-1.15)	

Abbreviations: ORs, Odds ratios; CIs, Confidence intervals; SNP, Single nucleotide polymorphisms

MV adjusted: age (years, continuous), sex (men, women), BMI (<23 and ≥23 kg/m^2), alcohol intake (never, ever for men; never, ever for women), smoking status (never, ever for HEXA, CAVAS, TWIN, never, pack-years <10, 10-<20, 20-<30, 30-<40 ≥40 for men; never, pack-years <5, 5-<10, ≥10 for women for KARE), education level (middle school or less, and high school or above), green tea intake (0-<2, and ≥2 cups/day), and total energy intake (kcal/day, continuous)

*Only the CAVAS and the KARE studies were included in analysis

3.2. Subgroup analysis on the association between coffee consumption and type 2 diabetes stratified by age, sex, BMI, smoking status, and alcohol drinking

Table 10 shows the ORs and 95% CIs of the risk of type 2 diabetes according to the dichotomous categories. The inverse association between coffee consumption and risk of type 2 diabetes persisted in subgroup analyses according to age, sex, BMI, smoking status, and alcohol intake; compared 0 to <0.5 cups/day of coffee consumption, ORs (95%CIs) with ≥3 cups/day of coffee consumption were 0.91 (0.80-1.02; *p* for trend=0.01) in <50 years, 0.91 (0.84-0.99; *p* for trend=0.11) in ≥50 years, 0.89 (0.81-0.97; *p* for trend=0.02) in men, 0.94 (0.85-1.04; *p* for trend=0.15) in women, 0.87 (0.79-0.96; *p* for trend<0.01) in BMI <25kg/m^2, 0.94 (0.86-1.02; *p* for trend=0.28) in BMI ≥25kg/$m^{2,}$ 0.93 (0.84-1.02; *p* for trend=0.18) in never smokers, 0.92 (0.83-1.01; *p* for trend=0.11) in non-drinkers, 0.91 (0.83-0.99; *p* for trend=0.04) in current drinkers. The inverse association did not vary by age, sex, BMI, smoking status, and alcohol drinking (*p* for interaction=0.97, 0.94, 0.34, 0.59, 0.93, respectively) .

Table 10. Odds Ratios (ORs) and 95% confidence intervals (CIs) for the risk of type 2 diabetes according to the dichotomous categories

		coffee consumption (cups/day)				*p* for trend	per 1 cup/day increment	*p* for interaction
		0 to <0.5	0.5 to <1	1 to <3	≥3			
Age at baseline (years)								0.97
<50	Case no.	355	131	559	311			
	Pooled OR (CIs)	1.00 (reference)	0.98 (0.84- 1.13)	0.92 (0.72- 1.17)	0.91 (0.81- 1.02)	0.01	0.96 (0.92-1.00)	
≥50	Case no.	1,080	332	1,334	498			
	Pooled OR (CIs)	1.00 (reference)	1.10 (1.00- 1.20)	1.01 (0.95- 1.07)	0.91 (0.84- 0.99)	0.11	0.98 (0.95-1.00)	
Sex								0.94
Men	Case no.	527	216	850	503			
	Pooled OR (CIs)	1.00 (reference)	1.06 (0.95- 1.20)	1.03 (0.96- 1.11)	0.89 (0.81- 0.97)	0.02	0.97 (0.94.1.00)	
Women	Case no.	908	247	1,043	306			
	Pooled OR (CIs)	1.00 (reference)	1.05 (0.95- 1.17)	0.97 (0.91- 1.04)	0.94 (0.85- 1.04)	0.15	0.98 (0.94-1.01)	
BMI (kg/m^2)								0.34
<25	Case no.	766	211	846	335			
	Pooled OR (CIs)	1.00 (reference)	1.06 (0.95- 1.19)	1.00 (0.92- 1.07)	0.87 (0.79- 0.96)	<0.01	0.96 (0.88-1.05)	
≥25	Case no.	669	252	1,046	473			
	Pooled OR (CIs)	1.00 (reference)	1.07 (0.96- 1.20)	1.01 (0.95- 1.09)	0.94 (0.86- 1.02)	0.28	0.99 (0.96-1.02)	

Table 10. Odds Ratios (ORs) and 95% confidence intervals (CIs) for the risk of type 2 diabetes according to the dichotomous categories (*Continued)*

		coffee consumption (cups/day)				*p* for trend	per 1 cup/day increment	*p* for interaction
		0 to <0.5	0.5 to <1	1 to <3	≥3			
Smoking status								0.59
Never	Case no.	1,011	290	1,197	341			
	Pooled OR (CIs)	1.00 (reference)	1.06 (0.96- 1.17)	1.01 (0.94- 1.07)	0.93 (0.84- 1.02)	0.18	0.98 (0.95-1.02)	
Ever	Case no.	411	169	689	466			
	Pooled OR (CIs)	1.00 (reference)	1.06 (0.92- 1.21)	0.99 (0.91- 1.08)	0.89 (0.81- 0.98)	0.01	0.96 (0.93-0.99)	
Alcohol drinking								
Non-drinker	Case no.	889	200	944	323			0.93
	Pooled OR (CIs)	1.00 (reference)	0.98 (0.87- 1.10)	1.06 (0.98- 1.14)	0.92 (0.83- 1.01)	0.11	0.97 (0.93-1.00)	
Current drinker	Case no.	540	260	941	483			
	Pooled OR (CIs)	1.00 (reference)	1.13 (1.02- 1.26)	0.96 (0.89- 1.03)	0.91 (0.83- 0.99)	0.04	0.98 (0.95-1.01)	

Abbreviations: ORs, Odds Ratios; CIs, confidence intervals; BMI, Body mass index

MV adjusted: age (years, continuous), sex (men, women), BMI (<18.5, 18.5- <23, 23-<25, and ≥25 kg/m^2), alcohol intake (never, ethanol g/day <10, 10-<20, 20-<30, 30-<40, 40-<50, 50-<60, ≥60 for men; never, ethanol g/d <10, 10<20, ≥20 for women for HEXA and KARE, never, ethanol g/day <10, 10-<20, 20-<30, 30-<40, ≥40 for men; never, ethanol g/d <10, ≥10 for women for CAVAS, and never, ethanol g/day <10, ≥10 for men; never, ever for women for TWIN), smoking status (never, pack-years <10, 10-<20, 20-<30, ≥30 for men; never, pack-years <5, 5-<10, ≥10 for women for HEXA, never, pack-years <10, 10-<20, 20-<30, ≥30 for men; never, pack-years <5, ≥5 for women for CAVAS, never, pack-years <10, 10-<20, 20-<30, 30-<40 ≥40 for men; never, pack-years <5, 5-<10, ≥10 for women for KARE, never, ever for men and never, ever for women for TWIN), regular exercise (no, physical activity frequency 1-2, 3-4, 5-6, and everyday per week for HEXA, CAVAS, TWIN, and tertile category in MET-h/wk for KARE), education level (elementary school or less, middle school, and high school or above), green tea intake (0-<1, 1-<2, and ≥2 cups/day), and total energy intake (kcal/day, continuous)

3.3. Subgroup analysis on the association between coffee consumption and type 2 diabetes by types of coffee consumed

Table 11 presents Odds Ratios (ORs) and 95% confidence intervals (CIs) for the risk of type 2 diabetes according to black coffee. Association between black coffee consumption and the risk of type 2 diabetes was not found. Compared to 0 to <0.5 cups/day of coffee consumption, pooled ORs (95% CIs) were 0.93 (0.69-1.24) for 0.5 to <1 cups/day of coffee consumption, 1.02 (0.67-1.55) for 1 to <3 cups/day of coffee consumption, 1.06 (0.86-1.31) for ≥3 cups/day of coffee consumption (*p* for trend=0.60).

Table 12 presents Odds Ratios (ORs) and 95% confidence intervals (CIs) for the risk of type 2 diabetes according to coffee with sugar and cream. Non-significant inverse association between black coffee consumption and the risk of type 2 diabetes was found. Compared to 0 to <0.5 cups/day of coffee consumption, pooled ORs (95% CIs) were 1.05 (0.92-1.19) for 0.5 to <1 cups/day of coffee consumption, 1.01 (0.94-1.09) for 1 to <3 cups/day of coffee consumption, 0.92 (0.83-1.02) for ≥3 cups/day of coffee consumption (*p* for trend=0.16). The association was inverse in each cohort; compared 0 to <0.5 cups/day of coffee consumption, ORs (95%CIs) with ≥3 cups/day of coffee consumption were 0.93 (0.82-1.04) in the HEXA, 0.84 (0.55-1.27) in the CAVAS, 0.89 (0.71-1.21) in the KARE, 1.34 (0.60-3.01) in the TWIN.

Table 11. Odds Ratios (ORs) and 95% confidence intervals (CIs) for the risk of type 2 diabetes according to black coffee

	Coffee consumption (cups/day)				*p* for trend	per 1 cup/day increment
	0 to <0.5	0.5 to <1	1 to <3	≥3		
HEXA						
Case/Total no.	2,568/47,820	40/930	172/3,610	84/1,687		
Age-sex adjusted	1.00 (reference)	0.87 (0.63-1.20)	0.98 (0.84-1.15)	1.06 (0.85-1.33)	0.79	1.02 (0.97-1.07)
MV adjusted	1.00 (reference)	0.88 (0.63-1.21)	0.97 (0.84-1.14)	1.03 (0.82-1.29)	0.99	1.01 (0.96-1.06)
CAVAS						
Case/Total no.	271/9,399	4/97	4/328	5/144		
Age-sex adjusted	1.00 (reference)	1.67 (0.61-4.60)	0.47 (0.17-1.28)	1.39 (0.56-3.44)	0.92	0.95 (0.74-1.22)
MV adjusted	1.00 (reference)	1.57 (0.57-4.35)	0.43 (0.16-1.18)	1.23 (0.49-3.05)	0.68	0.91 (0.71-1.18)
KARE						
Case/Total no.	1,296/5,344	7/30	43/154	13/45		
Age-sex adjusted	1.00 (reference)	1.09 (0.46-2.56)	1.46 (1.02-2.10)	1.54 (0.80-2.95)	0.03	1.11 (0.97-1.27)
MV adjusted	1.00 (reference)	0.96 (0.40-2.29)	1.46 (1.01-2.10)	1.29 (0.66-2.51)	0.08	1.08 (0.94-1.24)
Pooled						
MV adjusted	1.00 (reference)	0.93 (0.69-1.24)	1.02 (0.67-1.55)	1.06 (0.86-1.31)	0.60	1.01 (0.97-1.06)

Abbreviations: MV, Multivariate; ORs, Odds Ratios; CIs, confidence intervals; HEXA, Health Examinee; CAVAS, Cardiovascular Disease Association Study; KARE, the Korea Association Resource; TWIN, the Healthy Twin study

MV adjusted: age (years, continuous), sex (men, women), BMI (<18.5, 18.5- <23, 23-<25, and ≥25 kg/m^2), alcohol intake (never, ethanol g/day <10, 10-<20, 20-<30, 30-<40, 40-<50, 50-<60, ≥60 for men; never, ethanol g/d <10, 10<20, ≥20 for women for HEXA and KARE, never, ethanol g/day <10, 10-<20, 20-<30, 30-<40, ≥40 for men; never, ethanol g/d <10, ≥10 for women for CAVAS, and never, ethanol g/day <10, ≥10 for men; never, ever for women for TWIN), smoking status (never, pack-years <10, 10-<20, 20-<30, ≥30 for men; never, pack-years <5, 5-<10, ≥10 for women for HEXA, never, pack-years <10, 10-<20, 20-<30, ≥30 for men; never, pack-years <5, ≥5 for women for CAVAS, never, pack-years <10, 10-<20, 20-<30, 30-<40 ≥40 for men; never, pack-years <5, 5-<10, ≥10 for women for KARE, never/ever for men and never/ever for women for TWIN), regular exercise (no, physical activity frequency 1-2, 3-4, 5-6, and every day per week for HEXA, CAVAS, TWIN, and tertile in MET-h/wk for KARE), education level (elementary school or less, middle school, and high school or above), green tea intake (0-<1, 1-<2, and ≥2 cups/day), and total energy intake (kcal/day, continuous *the TWIN study was not included in the analysis due to insufficient case number

Table 12. Odds Ratios (ORs) and 95% confidence intervals (CIs) for the risk of type 2 diabetes according to coffee with sugar and cream

	Coffee consumption (cups/day)				*p* for trend	per 1 cup/day increment
	0 to <0.5	0.5 to <1	1 to <3	≥3		
HEXA						
Case/Total no.	1,415/27,557	197/3,345	846/15,536	406/7,609		
Age-sex agjusted	1.00 (reference)	1.13 (0.97-1.32)	1.04 (0.96-1.14)	1.01 (0.90-1.14)	0.79	1.01 (0.99-1.04)
MV adjusted	1.00 (reference)	1.20 (0.96-1.31)	1.01 (0.93-1.11)	0.93 (0.82-1.04)	0.23	0.99 (0.96-1.02)
CAVAS						
Case/Total no.	137/5,083	18/632	99/2,998	30/1,255		
Age-sex agjusted	1.00 (reference)	1.00 (0.61-1.65)	1.18 (0.90-1.53)	0.83 (0.55-1.25)	0.73	0.97 (0.88-1.06)
MV adjusted	1.00 (reference)	1.02 (0.62-1.68)	1.16 (0.88-1.51)	0.84 (0.55-1.27)	0.72	0.97 (0.88-1.07)
KARE						
Case/Total no.	729/2,957	89/393	405/1,666	136/557		
Age-sex agjusted	1.00 (reference)	0.88 (0.68-1.13)	0.98 (0.85-1.13)	0.98 (0.78-1.21)	0.85	0.97 (0.92-1.03)
MV adjusted	1.00 (reference)	0.88 (0.68-1.14)	0.97 (0.84-1.12)	0.89 (0.71-1.21)	0.38	0.95 (0.90-1.01)
TWIN						
Case/Total no.	26/828	6/165	14/417	12/287		
Age-sex agjusted	1.00 (reference)	1.01 (0.4-2.52)	1.12 (0.58-2.17)	1.58 (0.75-3.36)	0.28	1.16 (1-1.35)
MV adjusted	1.00 (reference)	0.98 (0.38-2.56)	1.05 (0.54-2.05)	1.34 (0.60-3.01)	0.49	1.14 (0.98-1.34)

Table 12. Odds Ratios (ORs) and 95% confidence intervals (CIs) for the risk of type 2 diabetes according to coffee with sugar and cream consumption (*Continued*)

	Coffee consumption (cups/day)				*p* for trend	per 1 cup/day increment
	0 to <0.5	0.5 to <1	1 to <3	≥3		
Pooled						
MV adjusted	1.00 (reference)	1.05 (0.92-1.19)	1.01 (0.94-1.09)	0.92 (0.83-1.02)	0.16	0.99 (0.96-1.01)

Abbreviations: MV, Multivariate; ORs, Odds Ratios; CIs, confidence intervals; HEXA, Health Examinee; CAVAS, Cardiovascular Disease Association Study; KARE, the Korea Association Resource; TWIN, the Healthy Twin study

MV adjusted: age (years, continuous), sex (men, women), BMI (<18.5, 18.5- <23, 23-<25, and ≥25 kg/m^2), alcohol intake (never, ethanol g/day <10, 10-<20, 20-<30, 30-<40, 40-<50, 50-<60, ≥60 for men; never, ethanol g/d <10, 10<20, ≥20 for women for HEXA and KARE, never, ethanol g/day <10, 10-<20, 20-<30, 30-<40, ≥40 for men; never, ethanol g/d <10, ≥10 for women for CAVAS, and never, ethanol g/day <10, ≥10 for men; never, ever for women for TWIN), smoking status (never, pack-years <10, 10-<20, 20-<30, ≥30 for men; never, pack-years <5, 5-<10, ≥10 for women for HEXA, never, pack-years <10, 10-<20, 20-<30, ≥30 for men; never, pack-years <5, ≥5 for women for CAVAS, never, pack-years <10, 10-<20, 20-<30, 30-<40 ≥40 for men; never, pack-years <5, 5-<10, ≥10 for women for KARE, never/ever for men and never/ever for women for TWIN), regular exercise (no, physical activity frequency 1-2, 3-4, 5-6, and every day per week for HEXA, CAVAS, TWIN, and tertile in MET-h/wk for KARE), education level (elementary school or less, middle school, and high school or above), green tea intake (0-<1, 1-<2, and ≥2 cups/day), and total energy intake (kcal/day, continuous)

V. Discussion

In this pooled analysis of 71,527 participants from 4 Korean prospective studies, consumption of ≥3 cups/day of coffee compared to 0 to <0.5 cups/day of coffee was associated with an 11% lower statistically significant risk of type 2 diabetes. The association between the coffee consumption and risk of type 2 diabetes did not vary by type 2 diabetes susceptibility genes.

This study finding is consistent with the inverse association between coffee consumption and risk of type 2 diabetes shown by other observational studies and meta-analyses performed in diverse countries (Carlstrom & Larsson, 2018; Odegaard et al., 2008; van Dam & Feskens, 2002; Yamaji et al., 2004). In a recent systematic review and meta-analysis, the pooled RR was 0.71 (95% CI = 0.67-0.76) in the highest category compared to the lowest category (Carlström & Larsson, 2018).

In this study no evidence of interaction with coffee consumption and risk of type 2 diabetes for *CDKAL1* rs7756992, *CDKN2A/B* rs10811661, *KCNJ11* rs5215, *KCNQ1* rs163184, and *PEPD* rs3786897 was suggested. In line with this study result, a previous study failed to find interaction between rs163184 in *KCNQ1* and coffee consumption in relation to type 2 diabetes (The InterAct Consortium, 2016). In this study no interaction with rs7756992 in *CDKAL1* (*p* for interaction= 0.56) was observed. However, our previous study found interaction between the risk-conferring G-allele of *CDKAL1* variants in coffee consumption and type 2 diabetes and prediabetes (Lee, Kim, Ahn, Yang, & Lee, 2015), but when we further expanded

our analysis to larger population, a significant interaction was not observed. Similarly, previous interaction findings for type 2 diabetes susceptibility genes, such as TCF7L2, GIPR, CAV2, and HFE, with other dietary factors were not replicated in the EPIC-InterACT study (Li et al., 2017). One possible reason for this discrepancy may be due to an inappropriate sample size that results in insufficiently powered statistical analysis (Sham & Purcell, 2014).

Genetic polymorphisms in *CDKAL1, CDKN2A/2B, KCNJ11, KCNQ1*, and *PEPD* that we selected as potential effect modifiers were found to be associated with type 2 diabetes in the East Asian population (Diabetes Genetics Replication and Meta-analysis Consortium, Asian Genetic Epidemiology Network Type 2 Diabetes Consortium, South Asian Type 2 Diabetes Consortium, Mexican American Type 2 Diabetes Consortium, & Type 2 Diabetes Genetic Exploration by Nex-generation sequencing in muylti-Ethnic Samples Consortium, 2014). *CDKAL1* and *CDKN2A/2B* have been associated with reduced insulin secretion by decreasing pancreatic β-cell function (Dimas et al., 2014; Pascoe et al., 2007). *CDKAL1* shares a considerable domain with *CDK5* regulator subunit-associated protein (CDK5 Rap1) (Wei et al., 2011). Because *CDK5* is implicated in insulin secretion in pancreatic β-cells, *CDKAL1* may regulate insulin secretion through interaction with *CDK5* (Wei et al., 2011; Wei et al., 2005). *PEPD* attenuated insulin-induced AKT2 phosphorylation resulting in increased insulin resistance (Chen et al., 2020). The potassium ion channels are responsible for the first phase if insulin secretion does not respond to glucose (Mandal, 2017). The potassium channel gene, *KCNJ11*

changed promoter methylation states in diabetic islets which impaired insulin secretion (Mandal, 2017). *KCNQ1* is expressed in tissues including the brain, adipose tissue, pancreas, and the insulin-secreting cell line INS-1 (Müssig et al., 2009). The risk allele of *KCNQ1* for type 2 diabetes is also associated with impaired insulin secretion, suggesting that the risk allele might confer susceptibility (Kasuga, 2011). Thus, the risk allele may influence the development of type 2 diabetes through the increased expression of *KCNQ1* in pancreatic β cells (Kasuga, 2011).

Coffee consumption has been associated with improved insulin sensitivity (van Dam, 2006). Given the many bioactive components in coffee, several mechanisms have suggested that coffee consumption might reduce the risk of type 2 diabetes. Chlorogenic acids are the major phenolic components in coffee and their hypoglycemic effects may be inhibiting glucose absorption and stimulate insulin secretion (Arion et al., 1997). Chlorogenic acid may suppress glucose release from the liver, and improve glucose uptake (Arion et al., 1997). In animal studies, consumption of chlorogenic acid has been shown to reduce fasting plasma glucose and increase insulin sensitivity (Ong, Hsu, & Tan, 2012). In addition, coffee contains several antioxidants, such as caffeine, chlorogenic acid, lignan, and melanoidins, which may suppress oxidative stress thus contributing to better metabolic control (Bloomer, Trepanowski, & Farney, 2013; Koloverou et al., 2015; Natella, Nardini, Giannetti, Dattilo, & Scaccini, 2002). Acute intake and long term coffee consumption have been demonstrated to lower oxidative stress in both human and animal studies (Bloomer et al., 2013; Koloverou et al., 2015; Natella et al., 2002).

Several components of coffee have been shown to have anti-inflammatory properties, such as caffeine, chlorogenic acid, and trigonelline (Natella & Scaccini, 2012; van Dam, 2006). Epidemiological and clinical studies have shown that coffee consumption may reduce the levels of pro-inflammatory biomarkers, such as interleukin(IL)-1b, IL-4, IL-6, IL-10, and C-reactive proteins, which can contribute to a reduced risk of type 2 diabetes (Imatoh et al., 2011; Natella & Scaccini, 2012; Williams et al., 2008).

The current pooled analysis had several limitations. First, measurement errors inherent in the dietary assessment may be present. However, several epidemiological studies have reported that coffee consumption by the FFQ is well measured with reasonable validity (Salvini et al., 1989; Tsubono, Kobayashi, Sasaki, & Tsugane, 2003). Second, the type of coffee consumed (caffeinated, decaffeinated) or brewing methods (unfiltered coffee or filtered coffee) were not assessed in the studies. However, there was an implication of consistent results despite the different coffee types (caffeinated, decaffeinated) or brewing methods (unfiltered coffee or filtered coffee) (Greenberg, Axen, Schnoll, & Boozer, 2005; Pereira, Parker, & Folsom, 2006; Tuomilehto, Hu, Bidel, Lindström, & Jousilahti, 2004; van Dam, Willett, Manson, & Hu, 2006). Third, the association between coffee and the incidence of type 2 diabetes was limited to examine at high levels of coffee consumption. Although coffee consumption was able to categorized up to 6 or 10 cups/day, ≥3cups/day was used as the highest level of coffee consumption because only a few participants reached up to 10 cups/day. This result may reflect the actual patterns of coffee

consumption among Koreans. Fourth, as an observational study, the potential for residual confounding could not be ruled out. However, possible confounding factors were adjusted including smoking and alcohol intake. Fifth, the high rate of failing to revisit the clinic for a health examination may be a concern. For the KARE study, approximately 90% of baseline participants completed at least one follow-up survey, but the rate of revisits to the clinic for a health examination decreased to 60% in the last sixth follow-up (Kim, Han, & Ko, 2017). For the HEXA, CAVAS, and TWIN studies, the rate of revisits to the clinic for a health examination decreased by approximately 40-60%. This may not be representative of the full cohort. Finally, causality cannot be established by the data from the observational studies alone.

The current analysis has several strengths. First, statistical power was increased by combining the results of 4 individual studies. Otherwise, the number of cases available for examination was insufficient to analyze the association of each cohort study. Second, potential confounding variables were modeled consistently and adjust to be study specific across the studies to attenuate any potential heterogeneity in the results. Third, a large sample size (n=71,527) was used in the Asian population.

In conclusion, coffee consumption was significantly associated with a reduced risk of type 2 diabetes incidence. Statistically significant interactions between coffee consumption and 5 SNPs related to type 2 diabetes were not observed (*CDKAL1* rs7756992, *CDKN2A/B* rs10811661, *KCNJ11* rs5215, *KCNQ1* rs163184, and *PEPD* rs3786897) in the association between coffee and the risk of type 2 diabetes. As Koreans have various types of coffee consumption, the classification of coffee types

in the data might need to be segmented to the type of coffee consumed. The present study suggests the importance of consumption ≥3 cups/day of coffee for risk of type 2 diabetes among Koreans. The study also emphasizes the need to replicate gene and diet interactions associated with type 2 diabetes in Asian populations.

References

Ahn, Y., Kwon, E., Shim, J. E., Park, M. K., Joo, Y., Kimm, K., Kim, D. H. (2007). Validation and reproducibility of food frequency questionnaire for Korean genome epidemiologic study. *Eur J Clin Nutr, 61*, 1435. doi:10.1038/sj.ejcn.1602657

American Diabetes Association. (2020). 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. *Diabetes Care, 43*(Suppl 1), S14-s31. doi:10.2337/dc20-S002

Arion, W. J., Canfield, W. K., Ramos, F. C., Schindler, P. W., Burger, H.-J., Hemmerle, H., Herling, A. W. (1997). Chlorogenic Acid and Hydroxynitrobenzaldehyde: New Inhibitors of Hepatic Glucose 6-Phosphatase. *Archives of Biochemistry and Biophysics, 339*(2), 315-322. doi:https://doi.org/10.1006/abbi.1996.9874

Bidel, S., Silventoinen, K., Hu, G., Lee, D. H., Kaprio, J., & Tuomilehto, J. (2008). Coffee consumption, serum gamma-glutamyltransferase and risk of type II diabetes. *Eur J Clin Nutr, 62*(2), 178-185. doi:10.1038/sj.ejcn.1602712

Bloomer, R. J., Trepanowski, J. F., & Farney, T. M. (2013). Influence of acute coffee consumption on postprandial oxidative stress. *Nutrition and metabolic insights, 6*, 35-42. doi:10.4137/NMI.S12215

Carlstrom, M., & Larsson, S. C. (2018). Coffee consumption and reduced risk of developing type 2 diabetes: a systematic review with meta-analysis. *Nutr*

Rev, 76(6), 395-417. doi:10.1093/nutrit/nuy014

Carlström, M., & Larsson, S. C. (2018). Coffee consumption and reduced risk of developing type 2 diabetes: a systematic review with meta-analysis. *Nutr Rev, 76*(6), 395-417. doi:10.1093/nutrit/nuy014

Chan, J. C., Malik, V., Jia, W., Kadowaki, T., Yajnik, C. S., Yoon, K. H., & Hu, F. B. (2009). Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *Jama, 301*(20), 2129-2140. doi:10.1001/jama.2009.726

Chen, Z., Yu, H., Shi, X., Warren, C. R., Lotta, L. A., Friesen, M., Cowan, C. A. (2020). Functional Screening of Candidate Causal Genes for Insulin Resistance in Human Preadipocytes and Adipocytes. *Circulation Research, 126*(3), 330-346. doi:doi:10.1161/CIRCRESAHA.119.315246

Cho, Y. S., Go, M. J., Kim, Y. J., Heo, J. Y., Oh, J. H., Ban, H.-J., Kim, H.-L. (2009). A large-scale genome-wide association study of Asian populations uncovers genetic factors influencing eight quantitative traits. *Nature genetics, 41*(5), 527-534. doi:10.1038/ng.357

Cochran, W. G. (1954). The Combination of Estimates from Different Experiments. *Biometrics, 10*(1), 101-129. doi:10.2307/3001666

Cornelis, M. C., & Hu, F. B. (2012). Gene-Environment Interactions in the Development of Type 2 Diabetes: Recent Progress and Continuing Challenges. *Annu Rev Nutr, 32*(1), 245-259. doi:10.1146/annurev-nutr-071811-150648

Costabile, A., Sarnsamak, K., & Hauge-Evans, A. C. (2018). Coffee, type 2

diabetes and pancreatic islet function – A mini-review. *Journal of Functional Foods, 45*, 409-416. doi:https://doi.org/10.1016/j.jff.2018.04.011

Diabetes Genetics Replication and Meta-analysis Consortium, Asian Genetic Epidemiology Network Type 2 Diabetes Consortium, South Asian Type 2 Diabetes Consortium, Mexican American Type 2 Diabetes Consortium, & Type 2 Diabetes Genetic Exploration by Nex-generation sequencing in muylti-Ethnic Samples Consortium. (2014). Genome-wide trans-ancestry meta-analysis provides insight into the genetic architecture of type 2 diabetes susceptibility. *Nature genetics, 46*(3), 234-244. doi:10.1038/ng.2897

Dietrich, S., Jacobs, S., Zheng, J.-S., Meidtner, K., Schwingshackl, L., & Schulze, M. B. (2019). Gene-lifestyle interaction on risk of type 2 diabetes: A systematic review. *Obesity Reviews, 20*(11), 1557-1571. doi:10.1111/obr.12921

Dimas, A. S., Lagou, V., Barker, A., Knowles, J. W., Mägi, R., Hivert, M.-F., Investigators, M. (2014). Impact of type 2 diabetes susceptibility variants on quantitative glycemic traits reveals mechanistic heterogeneity. *Diabetes, 63*(6), 2158-2171. doi:10.2337/db13-0949

Ding, M., Bhupathiraju, S. N., Chen, M., van Dam, R. M., & Hu, F. B. (2014). Caffeinated and decaffeinated coffee consumption and risk of type 2 diabetes: a systematic review and a dose-response meta-analysis. *Diabetes*

Care, 37(2), 569-586. doi:10.2337/dc13-1203

Greenberg, J. A., Axen, K. V., Schnoll, R., & Boozer, C. N. (2005). Coffee, tea and diabetes: the role of weight loss and caffeine. *Int J Obes (Lond), 29*(9), 1121-1129. doi:10.1038/sj.ijo.0802999

Imatoh, T., Tanihara, S., Miyazaki, M., Momose, Y., Uryu, Y., & Une, H. (2011). Coffee consumption but not green tea consumption is associated with adiponectin levels in Japanese males. *Eur J Nutr, 50*(4), 279-284. doi:10.1007/s00394-010-0136-5

International Diabetes Federation. (2017). *IDF Diabetes Atlas Eighth edition 2017*(8th ed ed.).

Jiang, X., Zhang, D., & Jiang, W. (2014). Coffee and caffeine intake and incidence of type 2 diabetes mellitus: a meta-analysis of prospective studies. *Eur J Nutr, 53*(1), 25-38. doi:10.1007/s00394-013-0603-x

Johnston, K. L., Clifford, M. N., & Morgan, L. M. (2003). Coffee acutely modifies gastrointestinal hormone secretion and glucose tolerance in humans: glycemic effects of chlorogenic acid and caffeine. *Am J Clin Nutr, 78*(4), 728-733. doi:10.1093/ajcn/78.4.728

Kasuga, M. (2011). KCNQ1, a susceptibility gene for type 2 diabetes. *J Diabetes Investig, 2*(6), 413-414. doi:10.1111/j.2040-1124.2011.00178.x

Kim, J., Kim, Y., Ahn, Y. O., Paik, H. Y., Ahn, Y., Tokudome, Y., Tajima, K. (2003). Development of a food frequency questionnaire in Koreans. *Asia Pac J Clin Nutr, 12*(3), 243-250.

Kim, Y., Han, B.-G., & Ko, G. E. S. g. (2017). Cohort Profile: The Korean Genome and Epidemiology Study (KoGES) Consortium. *International Journal of Epidemiology, 46*(2), e20-e20. doi:10.1093/ije/dyv316

Kim, Y. J., Go, M. J., Hu, C., Hong, C. B., Kim, Y. K., Lee, J. Y., consortium, M. (2011). Large-scale genome-wide association studies in east Asians identify new genetic loci influencing metabolic traits. *Nature genetics, 43*(10), 990-995. doi:10.1038/ng.939

Kim, Y. K., Moon, S., Hwang, M. Y., Kim, D. J., Oh, J. H., Kim, Y. J., Kim, B. J. (2013). Gene-based copy number variation study reveals a microdeletion at 12q24 that influences height in the Korean population. *Genomics, 101*(2), 134-138. doi:10.1016/j.ygeno.2012.11.002

Koloverou, E., Panagiotakos, D. B., Pitsavos, C., Chrysohoou, C., Georgousopoulou, E. N., Laskaris, A., & Stefanadis, C. (2015). The evaluation of inflammatory and oxidative stress biomarkers on coffee-diabetes association: results from the 10-year follow-up of the ATTICA Study (2002-2012). *Eur J Clin Nutr, 69*(11), 1220-1225. doi:10.1038/ejcn.2015.98

Korea Health Promotion Institute. (2013). Low-Risk Alcohol Drinking Guideline.

Korean Centers for Disease Control and Prevention. (2017). Korean Genome and Epidemiology Study user guideline.

Lee, J. K., Kim, K., Ahn, Y., Yang, M., & Lee, J. E. (2015). Habitual coffee intake, genetic polymorphisms, and type 2 diabetes. *Eur J Endocrinol, 172*(5),

595-601. doi:10.1530/eje-14-0805

Li, S. X., Imamura, F., Ye, Z., Schulze, M. B., Zheng, J., Ardanaz, E., Wareham, N. J. (2017). Interaction between genes and macronutrient intake on the risk of developing type 2 diabetes: systematic review and findings from European Prospective Investigation into Cancer (EPIC)-InterAct. *The American Journal Of Clinical Nutrition, 106*(1), 263-275. doi:10.3945/ajcn.116.150094

Mandal, S. S. (2017). *Gene Regulation, Epigenetics and Hormone Signaling*. Berlin, GERMANY: John Wiley & Sons, Incorporated.

Meng, S., Cao, J., Feng, Q., Peng, J., & Hu, Y. (2013). Roles of chlorogenic Acid on regulating glucose and lipids metabolism: a review. *Evid Based Complement Alternat Med, 2013*, 801457-801457. doi:10.1155/2013/801457

Ministry of Health and Welfare Korea Centers for Disease Control and Prevention. (2018). Korea Health Statistics 2016: Korea National Health and Nutrition Examination Survey (KNHANES VII-1). Retrieved from https://knhanes.cdc.go.kr/knhanes/sub04/sub04_03.do?classType=7

Ministry of Health and Welfare Korea Centers for Disease Control and Prevention. (2020). Korea Health Statistics 2018: Korea National Health and Nutrition Examination Survey (KNHANES VII-3). Retrieved from https://knhanes.cdc.go.kr/knhanes/sub04/sub04_03.do?classType%20=%207

Moon, S., Kim, Y. J., Han, S., Hwang, M. Y., Shin, D. M., Park, M. Y., Kim, B.-J. (2019). The Korea Biobank Array: Design and Identification of Coding Variants Associated with Blood Biochemical Traits. *Sci Rep, 9*(1), 1382. doi:10.1038/s41598-018-37832-9

Morris, A. P., Voight, B. F., Teslovich, T. M., Ferreira, T., Segrè, A. V., Steinthorsdottir, V., . . . Meta-analysis, C. (2012). Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. *Nature genetics, 44*(9), 981-990. doi:10.1038/ng.2383

Müssig, K., Staiger, H., Machicao, F., Kirchhoff, K., Guthoff, M., Schäfer, S. A., . . . Fritsche, A. (2009). Association of type 2 diabetes candidate polymorphisms in KCNQ1 with incretin and insulin secretion. *Diabetes, 58*(7), 1715-1720. doi:10.2337/db08-1589

Natella, F., Nardini, M., Giannetti, I., Dattilo, C., & Scaccini, C. (2002). Coffee drinking influences plasma antioxidant capacity in humans. *J Agric Food Chem, 50*(21), 6211-6216. doi:10.1021/jf025768c

Natella, F., & Scaccini, C. (2012). Role of coffee in modulation of diabetes risk. *Nutr Rev, 70*(4), 207-217. doi:10.1111/j.1753-4887.2012.00470.x

Noh, J. (2016). The Diabetes Epidemic in Korea. *Endocrinology and metabolism (Seoul, Korea), 31*(3), 349-353. doi:10.3803/EnM.2016.31.3.349

Odegaard, A. O., Pereira, M. A., Koh, W. P., Arakawa, K., Lee, H. P., & Yu, M. C. (2008). Coffee, tea, and incident type 2 diabetes: the Singapore Chinese

Health Study. *Am J Clin Nutr, 88*(4), 979-985. doi:10.1093/ajcn/88.4.979

Ong, K. W., Hsu, A., & Tan, B. K. (2012). Chlorogenic acid stimulates glucose transport in skeletal muscle via AMPK activation: a contributor to the beneficial effects of coffee on diabetes. *PLoS One, 7*(3), e32718. doi:10.1371/journal.pone.0032718

Orsini, N., Li, R., Wolk, A., Khudyakov, P., & Spiegelman, D. (2012). Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. *Am J Epidemiol, 175*(1), 66-73. doi:10.1093/aje/kwr265

Pascoe, L., Tura, A., Patel, S. K., Ibrahim, I. M., Ferrannini, E., Zeggini, E., Walker, M. (2007). Common Variants of the Novel Type 2 Diabetes Genes CDKAL1 and HHEX/IDE Are Associated With Decreased Pancreatic β-Cell Function. *Diabetes, 56*(12), 3101-3104. doi:10.2337/db07-0634

Peng, B. J., Zhu, Q., Zhong, Y. L., Xu, S. H., & Wang, Z. (2015). Chlorogenic Acid Maintains Glucose Homeostasis through Modulating the Expression of SGLT-1, GLUT-2, and PLG in Different Intestinal Segments of Sprague-Dawley Rats Fed a High-Fat Diet. *Biomed Environ Sci, 28*(12), 894-903. doi:10.3967/bes2015.123

Pereira, M. A., Parker, E. D., & Folsom, A. R. (2006). Coffee consumption and risk of type 2 diabetes mellitus: an 11-year prospective study of 28 812 postmenopausal women. *Arch Intern Med, 166*(12), 1311-1316. doi:10.1001/archinte.166.12.1311

Saeedi, P., Petersohn, I., Salpea, P., Malanda, B., Karuranga, S., Unwin, N., Williams, R. (2019). Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract, 157*. doi:10.1016/j.diabres.2019.107843

Salvini, S., Hunter, D. J., Sampson, L., Stampfer, M. J., Colditz, G. A., Rosner, B., & Willett, W. C. (1989). Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. *Int J Epidemiol, 18*(4), 858-867. doi:10.1093/ije/18.4.858

Sham, P. C., & Purcell, S. M. (2014). Statistical power and significance testing in large-scale genetic studies. *Nat Rev Genet, 15*(5), 335-346. doi:10.1038/nrg3706

The InterAct Consortium. (2016). Investigation of gene–diet interactions in the incretin system and risk of type 2 diabetes: the EPIC-InterAct study. *Diabetologia, 59*(12), 2613-2621. doi:10.1007/s00125-016-4090-5

Thompson, S. G., & Higgins, J. P. (2002). How should meta-regression analyses be undertaken and interpreted? *Stat Med, 21*(11), 1559-1573. doi:10.1002/sim.1187

Tsubono, Y., Kobayashi, M., Sasaki, S., & Tsugane, S. (2003). Validity and Reproducibility of a Self-administered Food Frequency Questionnaire Used in the Baseline Survey of the JPHC Study Cohort I. *Journal of Epidemiology, 13*(1sup), 125-133. doi:10.2188/jea.13.1sup_125

Tuomilehto, J., Hu, G., Bidel, S., Lindström, J., & Jousilahti, P. (2004). Coffee consumption and risk of type 2 diabetes mellitus among middle-aged Finnish men and women. *Jama, 291*(10), 1213-1219. doi:10.1001/jama.291.10.1213

van Dam, R. M. (2006). Coffee and type 2 diabetes: From beans to beta-cells. *Nutrition, Metabolism and Cardiovascular Diseases, 16*(1), 69-77. doi:https://doi.org/10.1016/j.numecd.2005.10.003

van Dam, R. M., & Feskens, E. J. (2002). Coffee consumption and risk of type 2 diabetes mellitus. *Lancet, 360*(9344), 1477-1478. doi:10.1016/s0140-6736(02)11436-x

van Dam, R. M., & Hu, F. B. (2005). Coffee consumption and risk of type 2 diabetes: a systematic review. *Jama, 294*(1), 97-104. doi:10.1001/jama.294.1.97

van Dam, R. M., Willett, W. C., Manson, J. E., & Hu, F. B. (2006). Coffee, caffeine, and risk of type 2 diabetes: a prospective cohort study in younger and middle-aged U.S. women. *Diabetes Care, 29*(2), 398-403. doi:10.2337/diacare.29.02.06.dc05-1512

Wei, F.-Y., Suzuki, T., Watanabe, S., Kimura, S., Kaitsuka, T., Fujimura, A., Tomizawa, K. (2011). Deficit of tRNA(Lys) modification by Cdkal1 causes the development of type 2 diabetes in mice. *The Journal of clinical investigation, 121*(9), 3598-3608. doi:10.1172/JCI58056

Wei, F. Y., Nagashima, K., Ohshima, T., Saheki, Y., Lu, Y. F., Matsushita, M.,

Tomizawa, K. (2005). Cdk5-dependent regulation of glucose-stimulated insulin secretion. *Nat Med, 11*(10), 1104-1108. doi:10.1038/nm1299

Williams, C. J., Fargnoli, J. L., Hwang, J. J., van Dam, R. M., Blackburn, G. L., Hu, F. B., & Mantzoros, C. S. (2008). Coffee Consumption Is Associated With Higher Plasma Adiponectin Concentrations in Women With or Without Type 2 Diabetes. *A prospective cohort study, 31*(3), 504-507. doi:10.2337/dc07-1952

Yamaji, T., Mizoue, T., Tabata, S., Ogawa, S., Yamaguchi, K., Shimizu, E., Kono, S. (2004). Coffee consumption and glucose tolerance status in middle-aged Japanese men. *Diabetologia, 47*(12), 2145-2151. doi:10.1007/s00125-004-1590-5

Zhou, J., Zhou, S., & Zeng, S. (2013). Experimental diabetes treated with trigonelline: effect on β cell and pancreatic oxidative parameters. *Fundamental & Clinical Pharmacology, 27*(3), 279-287. doi:10.1111/j.1472-8206.2011.01022.x

국문초록

커피 섭취, 유전적 다형성과 제2형 당뇨병과의 연관성: 한국인 코호트 통합연구

서울대학교 대학원 식품영양학과

김안나

당뇨병은 전 세계적으로 중요한 건강 문제로 대두되고 있다. 커피는 전 세계적으로 널리 소비되고 있으며, 커피의 주성분인 폴리페놀 화합물이 제2형 당뇨병을 예방할 수 있을 것이라는 점에서 점차 주목받고 있다. 메타 분석 결과 커피를 하루에 한잔씩 섭취할수록 제2형 당뇨병 발생의 위험이 3% 낮은 것으로 보고되었다. 식이 요인 이외에도 유전적 요인이 제2형 당뇨병 발생에 기여할 것으로 알려졌으며, 이에 따라 유전자 다형성과 당뇨병 감수성(susceptibility)에 관한 연구가 활발히 진행되어 왔다. 본 연구에서는 커피 섭취가 당뇨병 발생과 연관이 있는지 확인하고, 이 연관성이 제2형 당뇨병 감수성 유전자에 의해 변화가 있는지 살펴보았다. 따라서, 본 연구에서는 한국인 유전체 역학조사 사업(Korean Genome and Epidemiology Study: KoGES)에

포함된 4개의 한국인 코호트 연구에서(도시기반 코호트 The Health Examinees: HEXA study; 농촌 기반 코호트 the Cardiovascular Disease Association Study: CAVAS; 지역사회 기반 코호트 the Korea Association Resource: KARE study; 쌍둥이 가족 코호트 the Healthy Twin: TWIN study) 총 71,527명의 대상자가 본 연구에 포함되어 커피 섭취와 당뇨병 발생과의 연관성, 제2형 당뇨병 감수성 유전자로 밝혀진 5개의 유전자(*CDKAL1* rs7756992, *CDKN2A/B* rs10811661, *KCNJ11* rs5215, *KCNQ1* rs163184, *PEPD* rs3786897)에 의한 상호작용 분석을 수행하였다. 미국당뇨병학회(the American Diabetes Association: ADA)의 제2형 당뇨병 기준에 따라 1) 공복혈당 ≥126 mg/dL, 2) 당화혈색소 ≥6.5%, 3) 경구당부하검사 ≥200 mg/dL 에 해당하거나, 4) 당뇨병을 진단 받은 적 있다고 자가 보고한 경우 또는 5) 현재 저혈당 약물을 복용 하는 경우를 당뇨병으로 분류 하였다. 커피의 섭취 빈도와 섭취 분량을 이용하여 하루 커피 섭취량(cups/day)을 계산하였고, 하루 0.5잔 미만, 0.5 이상 ~ 1잔 미만, 1잔 이상 ~ 2잔 미만, 3잔 이상으로 범주화 하였다. 로지스틱 회귀분석을 통해 4개의 각 코호트 연구에서 당뇨병 발생에 대한 커피 섭취의 오즈비(odds ratios: ORs)와 95% 신뢰구간을 추정하였다. 분석에 포함된 연구들 간의 이질성 여부에 따라 이질성이 있는 경우에는 랜덤 효과 모형(random-

effect model), 이질성이 없는 경우에는 고정효과모형(fixed-effect model)을 이용하여 통합 분석(pooled analysis)을 수행하였다. 이 때, 연구들 간의 이질성 여부를 확인하기 위해 Cochran's Q test를 사용하였다. 삼차분석 모델(restricted cubic spline model)을 사용하여 커피 섭취량의 구간을 세분화하고 구간 별 추정된 회귀 계수를 확인하여 선형성을 검정하였다. 인구통계학적 특성, 생활습관 요인 및 위의 5가지 SNPs에 따른 하위 집단 분석(subgroup analysis)을 수행하였으며, meta-regression을 통해 유의한 상호작용이 있는지 확인하였다. 4개의 코호트 연구에서 커피 섭취량이 많을수록 연령이 낮고, 남성의 비율이 높았으며, 높은 교육수준, 흡연량 및 음주량을 보였고, 녹차 및 총 에너지 섭취량이 더 높은 것으로 나타났다. 4개의 코호트 연구 결과를 통합 분석한 결과, 하루 0.5잔 미만의 커피를 마시는 그룹에 비해 하루 3잔 이상 마시는 그룹에서 제2형 당뇨병의 발생 위험이 11% 낮았다 (pooled OR=0.89 [95% CI=0.80-0.98] p for trend=0.01). 또한, 커피를 하루에 한잔씩 섭취할수록 제2형 당뇨병 발생의 위험이 3% 낮았다 (pooled OR=0.97 [95% CI=0.95-1.00]). 당뇨병 감수성 유전자로 알려져 있는 5개의 SNPs (*CDKAL1* rs7756992, *CDKN2A/B* rs10811661, *KCNJ11* rs5215, *KCNQ1* rs163184, *PEPD* rs3786897)로 층화하여 우성모델(dominant model)로 분석하였을 때,

각 하위 그룹에서 모두 하루 0.5잔 미만의 커피를 마시는 그룹에 비해 하루 3잔 이상 마시는 그룹에서 제2형 당뇨병의 발생 위험이 낮은 것으로 나타났으나 유의하지 않았고, 유의한 상호작용 또한 나타나지 않았다(p for interaction=0.56, 0.97, 0.73, 0.62, 0.68). 그 외에 연령, 성별, BMI, 흡연 여부, 음주 여부에 따라 층화하여 상호작용 분석을 수행하였지만 모두 유의한 상호작용이 없는 것으로 나타났다(p for interaction=0.97, 0.94, 0.34, 0.59, 0.93). 본 연구에서는 4개의 한국인 코호트 연구를 통합 분석한 결과, 커피 섭취가 제2형 당뇨병 발생의 위험을 감소시키는 것을 확인할 수 있었고, 당뇨병 감수성 유전자에 따라서는 상호작용이 없는 것으로 나타났다. 이에 따라, 커피 섭취가 제2형 당뇨병 발생 감소에 기여할 수 있을 것으로 여겨지며, 이 근거를 뒷받침 할 수 있는 기전적인 연구 및 추가적인 유전자 상호작용 연구가 필요할 것으로 사료된다.

주요어: 커피 섭취; 제2형 당뇨; 유전적 다형성; 코제스; 통합 분석;

학번: 2018-23665