SUPPLEMENTARY DATA

Supplementary Table 1. Characteristics of genetic variants associated with T2DM in the UK biobank

Chromosome	Nearest Gene	Rs number	Effective allele	Non-effective allele	Odds ratios	95 %, CI for Odds ratios
14	*NRXN3*	rs10146997	G	A	1.07	1.04-1.10
2	*BCL11A*	rs10193447	T	C	1.07	1.05-1.10
7	*PAX4*	rs10229583	G	A	1.04	1.01-1.07
7	*DGKB*	rs10238625	A	G	1.07	1.04-1.09
7	*DGKB*	rs10276674	C	T	1.09	1.06-1.12
11	*HSD17B12*	rs1061810	A	C	1.08	1.05-1.11
9	*CDKN2A/B*	rs10757282	C	T	1.04	1.01-1.06
9	*GLIS3*	rs10758593	A	G	1.05	1.02-1.07
11	*MTNR1B*	rs10830963	G	C	1.08	1.05-1.11
10	*GRK5*	rs10886471	C	T	1.02	0.99-1.04
7	*KLF14*	rs10954284	T	A	1.06	1.03-1.08
9	*CDKN2A/B*	rs10965223	A	G	1.08	1.05-1.11
9	*CDKN2A/B*	rs10965248	T	C	1.15	1.11-1.18
10	*VPS26A*	rs10998572	C	A	1.09	1.04-1.15
12	*CCND2*	rs11063018	C	T	1.09	1.06-1.13
2	*CCDC85A*	rs1116357	G	A	1.01	0.99-1.04
10	*HHEX/IDE*	rs11187140	G	A	1.14	1.11-1.17
13	*SPRY2*	rs11616380	G	T	1.09	1.07-1.12
3	*ADCY5*	rs11708067	A	G	1.12	1.08-1.15
3	*PPARG*	rs11712037	C	G	1.14	1.10-1.18
6	*CENPW*	rs11759026	G	A	1.1	1.06-1.13
8	*TP53INP1*	rs11786613	C	A	1.21	1.12-1.31
7	*MNX1*	rs1182436	C	T	1.08	1.05-1.12
1	*FAF1*	rs12031920	T	A	1.05	1.03-1.08
18	*BCL2A*	rs12454712	T	C	1.05	1.02-1.08
15	*PRC1*	rs12595616	C	T	1.07	1.04-1.09
20	*HNF4A*	rs12625671	C	T	1.09	1.05-1.13
9	*TLE4*	rs13301067	G	A	1.11	1.06-1.16
4	*MAEA*	rs1531583	T	G	1.15	1.08-1.22
16	*FTO*	rs1558902	A	T	1.13	1.11-1.16
2	*RBMS1*	rs1563575	A	G	1.07	1.04-1.10
9	*DMRTA1*	rs1575972	T	A	1.13	1.05-1.21
7	*JAZF1*	rs1635852	T	C	1.1	1.07-1.12
5	*ANKRD55*	rs173964	G	A	1.06	1.03-1.09

20	*HNF4A*	rs1800961	T	C	1.17	1.09-1.25
2	*DNER*	rs1861612	A	G	1.02	1.00-1.05
18	*MC4R*	rs1942880	T	C	1.07	1.04-1.10
22	*MTMR3/HORMAD 2*	rs2023681	G	A	1.13	1.09-1.18
6	*HLA-B*	rs2244020	G	A	1.02	1.00-1.05
12	*HMGA2*	rs2258238	T	A	1.11	1.07-1.16
10	*PLEKHA1*	rs2292626	C	T	1.09	1.06-1.11
11	*KCNQ1*	rs231360	T	C	1.08	1.05-1.11
11	*KCNQ1*	rs233449	G	A	1.09	1.06-1.12
11	*DUSP8*	rs2334499	T	C	1.05	1.03-1.08
12	*MPHOSPH9*	rs2851437	A	C	1.07	1.04-1.10
2	*GRB14*	rs28584669	T	C	1.05	1.02-1.09
16	*CMIP*	rs2925979	T	C	1.08	1.05-1.10
1	*PROX1*	rs340874	C	T	1.07	1.04-1.10
3	*UBE2E2*	rs35352848	T	C	1.09	1.06-1.12
1	*MACF1*	rs3768321	T	G	1.08	1.05-1.11
8	*SLC30A8*	rs3802177	G	A	1.12	1.09-1.15
4	*WFS1*	rs3821943	T	C	1.1	1.08-1.13
1	*NOTCH2*	rs406767	C	T	1.14	1.08-1.20
12	*CCND2*	rs4238013	C	T	1.1	1.07-1.14
19	*APOE*	rs429358	T	C	1.13	1.09-1.17
3	*IGF2BP2*	rs4402960	T	G	1.15	1.12-1.18
11	*KCNQ1*	rs441613	C	T	1.06	1.03-1.08
8	*TP53INP1*	rs4734285	T	C	1.06	1.03-1.08
15	*C2CD4A*	rs4774420	C	T	1.08	1.05-1.11
8	*ANK1*	rs516946	C	T	1.08	1.04-1.11
11	*KCNJ11*	rs5219	T	C	1.07	1.04-1.10
19	*GIPR*	rs55864746	A	G	1.07	1.04-1.10
12	*HNF1A (TCF1)*	rs56348580	G	C	1.08	1.05-1.10
19	*CILP2*	rs58489806	T	C	1.09	1.04-1.13
4	*ACSL1*	rs60780116	T	C	1.09	1.06-1.13
15	*ZFAND6*	rs62006309	A	G	1.05	1.03-1.08
9	*ABO*	rs635634	T	C	1.08	1.05-1.12
5	*ZBED3*	rs6453287	C	A	1.07	1.04-1.09
12	*TSPAN8/LGR5*	rs6581998	C	T	1.06	1.03-1.09

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1	*ATP8B2*	rs67156297	A	G	1.03	1.00-1.06
2	*TMEM163*	rs6723108	T	G	1.02	1.00-1.05
2	*THADA*	rs6757251	C	T	1.14	1.10-1.19
3	*LPP*	rs6777684	G	A	1.05	1.03-1.08
15	*INAFM2*	rs67839313	C	T	1.03	0.99-1.07
6	*SLC35D3*	rs6918311	A	G	1.07	1.04-1.10
6	*SSR1/RREB1*	rs6923241	C	T	1.07	1.04-1.10
11	*MIR4686*	rs7107784	G	A	1.02	0.99-1.05
17	*ZZEF1*	rs7224685	T	G	1.07	1.04-1.10
18	*LAMA1*	rs7234111	C	T	1.06	1.04-1.09
13	*TBC1D4*	rs7330796	C	T	1.02	0.98-1.06
15	*RASGRP1*	rs7403531	T	C	1.04	1.01-1.07
3	*ADAMTS9*	rs7428936	T	C	1.07	1.05-1.10
6	*CDKAL1*	rs7451008	C	T	1.19	1.16-1.22
5	*PAM*	rs74944275	T	C	1.16	1.09-1.24
11	*KCNQ1*	rs756852	G	A	1.09	1.06-1.13
17	*HNF1B (TCF2)*	rs757209	G	A	1.09	1.06-1.12
11	*ARAP1 (CENTD2)*	rs76550717	A	G	1.1	1.07-1.14
4	*TMEM154*	rs7660590	C	T	1.06	1.03-1.08
17	*GLP2R*	rs78761021	G	A	1.07	1.05-1.10
10	*TCF7L2*	rs7903146	T	C	1.34	1.31-1.38
7	*MIR129-LEP*	rs791595	G	A	1.01	0.98-1.04
12	*KLHDC5*	rs7953190	T	C	1.08	1.05-1.11
16	*BCAR1*	rs8056814	G	A	1.16	1.11-1.22
10	*ZMIZ1*	rs810517	C	T	1.09	1.07-1.12
7	*GCK*	rs878521	A	G	1.05	1.02-1.08
6	*HLA-DQA1*	rs9271774	C	A	1.1	1.06-1.14
2	*ASB3*	rs9309245	G	C	1.01	0.98-1.04
9	*TLE1*	rs9410573	T	C	1.08	1.05-1.10
15	*HMG20A*	rs952471	G	C	1.08	1.06-1.11
5	*ANKRD55*	rs9687833	A	G	1.1	1.07-1.13
3	*ST6GAL1*	rs9820223	C	T	1.06	1.03-1.09
17	*SRR*	rs9911305	A	G	1.05	1.02-1.07

Beta value =Ln (OR)

SUPPLEMENTARY DATA

Supplementary Table 2. Definitions of prevalent diabetes and incident T2D.

	Source and definition	UK Biobank field code
Diabetes at baseline [Both "possible" diabetes (T1D, T2D and other types of diabetes) and "probable" diabetes (T1D, T2D and other types of diabetes) were excluded at baseline.]	Self-reported at baseline [1]; Medication for diabetes at baseline [1]; ICD9: 250, 6480 (if incident time of diabetes<=Date of attending assessment centre); ICD10: E10, E11, E12, E13, E14, O24 (if incident time of diabetes<= Date of attending assessment centre).	20002, 20003, 2976, 6153, 6177 41271, 41281, 41270, 41280, 53, 191,40000
Incident T2D	ICD 10: E11	41270,41280

1. Eastwood SV, Mathur R, Atkinson M, et al. Algorithms for the capture and adjudication of prevalent and incident diabetes in UK Biobank. PLoS One. 2016. 11(9): e0162388.

SUPPLEMENTARY DATA

Supplementary Table 3. Hazard ratios (HRs) for T2DM across quartiles (Q) categories of T2DM-GRS

	Quartiles (Q) categories of T2DM-GRS				
	Q1	Q2	Q3	Q4	*P*-trend
T2DM, Case, n (%)	942 (1.0)	1318 (1.5)	1627 (1.8)	2113 (2.3)	
Model 1	1 (reference)	1.41 (1.29-1.53)	1.74 (1.61-1.89)	2.29 (2.13-2.48)	<0.001
Model 2	1 (reference)	1.38 (1.27-1.50)	1.72 (1.59-1.87)	2.27 (2.11-2.46)	<0.001

Model 1: Results were adjusted for age, sex, the first 10 genetic principal components and genotyping array.
Model 2: Results were adjusted for age, sex, centers, BMI, physical activity, smoking, moderate drinking, healthy diet, Townsend deprivation index, aspirin use, Non-aspirin NSAIDs use, family history of diabetes, arthritis, hypertension, high cholesterol, vitamin supplement use, mineral supplement use, the first 10 genetic principal components and genotyping array.

SUPPLEMENTARY DATA

Supplementary Table 4. The Hazard ratios of glucosamine use for T2DM after excluding participants with glucose level ≥ 7.0 (mmol/L).

	Non-glucosamine user	Glucosamine user	*P*-value
Case, n (%)	5368 (1.7)	1188 (1.5)	
Age and sex-adjusted HR (95% CI)	1 (reference)	0.83 (0.78-0.88)	<0.001
Model 1	1 (reference)	0.82 (0.76-0.87)	<0.001
Model 2	1 (reference)	0.84 (0.79-0.90)	<0.001

Model 1: Results were adjusted for age, sex, race, centers, BMI, physical activity, smoking, healthy diet, Townsend deprivation index, aspirin use, Non-aspirin NSAIDs use, family history of diabetes, osteoarthritis or joint, hypertension, high cholesterol and fasting time.
Model 2: further adjustment for vitamin supplement use and mineral supplement use on the basis of model 1.

SUPPLEMENTARY DATA

Supplementary Table 5. The Hazard ratios of glucosamine use for T2DM after excluding participants with HbA1c levels ≥ 48 (mmol/mol).

	Non-glucosamine user	Glucosamine user	*P*-value
Case, n (%)	4309 (1.6)	953 (1.4)	
Age and sex-adjusted HR (95% CI)	1 (reference)	0.83 (0.77-0.88)	<0.001
Model 1	1 (reference)	0.82 (0.76-0.87)	<0.001
Model 2	1 (reference)	0.84 (0.79-0.91)	<0.001

Model 1: Results were adjusted for age, sex, race, centers, BMI, physical activity, smoking, healthy diet, Townsend deprivation index, aspirin use, Non-aspirin NSAIDs use, family history of diabetes, osteoarthritis or joint, hypertension and high cholesterol.
Model 2: further adjustment for vitamin supplement use and mineral supplement use on the basis of model 1.

SUPPLEMENTARY DATA

Supplementary Table 6. The Hazard ratios of glucosamine use for T2DM after excluding participants with limited follow-up years (≦2 years).

	Non-glucosamine user	Glucosamine user	*P*-value
Case, n (%)	4498 (1.5)	1012 (1.4)	
Age and sex-adjusted HR (95% CI)	1 (reference)	0.84 (0.79-0.90)	<0.001
Model 1	1 (reference)	0.82 (0.76-0.88)	<0.001
Model 2	1 (reference)	0.84 (0.78-0.90)	<0.001

Model 1: Results were adjusted for age, sex, race, centers, BMI, physical activity, smoking, healthy diet, Townsend deprivation index, aspirin use, Non-aspirin NSAIDs use, family history of diabetes, osteoarthritis or joint, hypertension and high cholesterol.
Model 2: further adjustment for vitamin supplement use and mineral supplement use on the basis of model 1.

SUPPLEMENTARY DATA

Supplementary Table 7. The Hazard ratios of glucosamine use for T2DM after excluding participants who regular take anti-inflammatory drugs (aspirin use or Non-aspirin NSAIDs use)

	Non-glucosamine user	Glucosamine user	*P*-value
Case, n (%)	4198 (1.7)	853 (1.5)	
Age and sex-adjusted HR (95% CI)	1 (reference)	0.81 (0.76-0.88)	<0.001
Model 1	1 (reference)	0.80 (0.74-0.86)	<0.001
Model 2	1 (reference)	0.82 (0.76-0.89)	<0.001

Model 1: Results were adjusted for age, sex, race, centers, BMI, physical activity, smoking, healthy diet, Townsend deprivation index, family history of diabetes, osteoarthritis or joint, hypertension and high cholesterol.
Model 2: further adjustment for vitamin supplement use and mineral supplement use on the basis of model 1.

SUPPLEMENTARY DATA

Supplementary Table 8. The Hazard ratios of glucosamine use for T2DM after further adjusted for glucose levels or HbA1c levels or CRP levels.

	Non-glucosamine user	Glucosamine user	*P*-value
Case, n (%)	5138 (1.8)	1120 (1.7)	
Model 1+glucose+fasting time	1 (reference)	0.86 (0.80-0.92)	
Case, n (%)	5539 (1.8)	1213 (1.6)	
Model 1+HbA1c	1 (reference)	0.86 (0.80-0.92)	<0.001
Case, n (%)	5543 (1.8)	1225 (1.7)	
Model 1+CRP	1 (reference)	0.86 (0.80-0.92)	<0.001

Model 1: Results were adjusted for age, sex, race, centers, BMI, physical activity, smoking, healthy diet, Townsend deprivation index, aspirin use, Non-aspirin NSAIDs use, family history of diabetes, osteoarthritis or joint, hypertension, high cholesterol, vitamin supplement use and mineral supplement use.

SUPPLEMENTARY DATA

Supplementary Table 9. The Hazard ratios of habitual glucosamine use for T2DM in the UK biobank. [Analysis were conducted in participants who provide information in "Vitamin/mineral supplements yesterday" questionnaire at least once during the follow-up period.]

	Non-glucosamine user	Non-habitual glucosamine user [a,b]	Habitual glucosamine user [a,c]	*P*-trend
Case, n (%)	1414 (1.3)	232 (1.3)	224 (1.1)	
Model 1	1 (reference)	0.96 (0.83-1.12)	0.75 (0.64-0.88)	<0.001
Model 2	1 (reference)	0.85 (0.73-0.99)	0.75 (0.63-0.88)	<0.001

Model 1: Results were adjusted for age and sex

Model 2: Results were adjusted for age, sex, race, centers, BMI, physical activity, smoking, healthy diet, Townsend deprivation index, aspirin use, Non-aspirin NSAIDs use, family history of diabetes, arthritis, hypertension, high cholesterol, vitamin supplement use and mineral supplement use.

[a] "Vitamin/mineral supplements yesterday" questionnaire only provide the "glucosamine/chondroitin" as an optional item (At baseline, questionnaire only provide the "glucosamine" as an optional item). However, because glucosamine and chondroitin supplements are usually taken together in one pill, chondroitin is rarely taken alone by individuals (In the Nurses' Health Study and Health Professionals follow-up study, nearly all (97–98%) chondroitin users also reported use of glucosamine), we assumed that questions on the glucosamine use were equivalent in the sensitivity analyses.

[b] Participants who indicated they took glucosamine only once at baseline or during the follow-up (1 baseline survey + 4 times of "Vitamin/mineral supplements yesterday" surveys).

[c] participants who indicated they took glucosamine at least two times at baseline or during the follow-up period.

SUPPLEMENTARY DATA

Supplementary Figure 1A. The joint association of glucosamine use and CRP in relation to risk of T2D (after excluding participants with high glucose levels).

Results were adjusted for age, sex, race, centers, BMI, physical activity, smoking, healthy diet, Townsend deprivation index, moderate drinking, aspirin use, Non-aspirin NSAIDs use, family history of diabetes, osteoarthritis or joint pain, hypertension, high cholesterol, vitamin supplement use, mineral supplement use and fasting time.

Supplementary Figure 1B. The joint association of glucosamine use and CRP in relation to risk of T2D (after excluding participants with high HbA1c levels).

Results were adjusted for age, sex, race, centers, BMI, physical activity, smoking, healthy diet, Townsend deprivation index, moderate drinking, aspirin use, Non-aspirin NSAIDs use, family history of diabetes, osteoarthritis or joint pain, hypertension, high cholesterol, vitamin supplement use and mineral supplement use.

Supplementary Figure 1C. The joint association of glucosamine use and CRP in relation to risk of T2D (after excluding participants with limited follow-up years ($\leqq$ 2 years)).

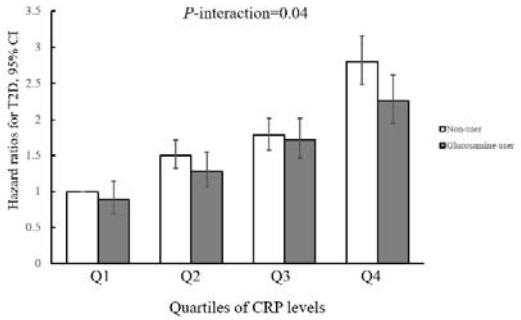
Results were adjusted for age, sex, race, centers, BMI, physical activity, smoking, healthy diet, Townsend deprivation index, moderate drinking, family history of diabetes, osteoarthritis or joint pain, hypertension, high cholesterol, vitamin supplement use and mineral supplement use.

Supplementary Figure 1D. The joint association of glucosamine use and CRP in relation to risk of T2D (after excluding participants who regular took anti-inflammatory drug).

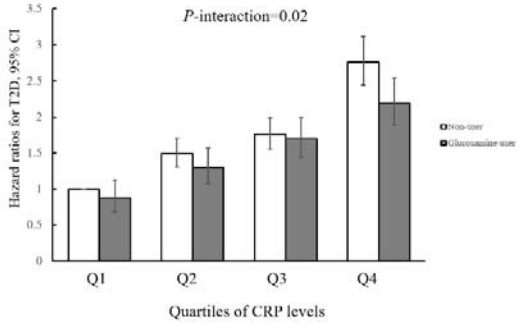
Results were adjusted for age, sex, race, centers, BMI, physical activity, smoking, healthy diet, Townsend deprivation index, moderate drinking, family history of diabetes, osteoarthritis or joint pain, hypertension, high cholesterol, vitamin supplement use and mineral supplement use.

SUPPLEMENTARY DATA

Supplementary figure 1A



Supplementary figure 1B



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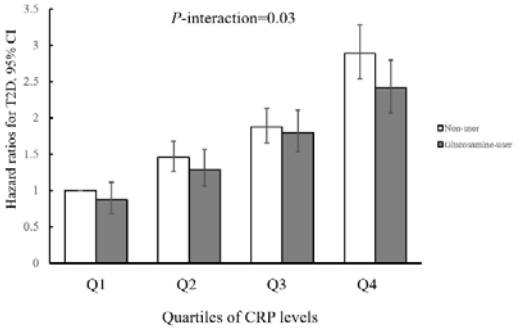
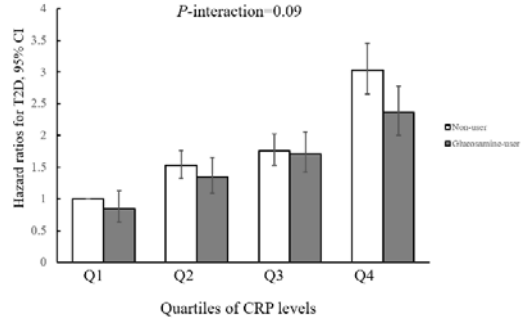


Supplementary figure 1D



SUPPLEMENTARY DATA

Supplementary materials

Details of covariates

Height was measured by a Seca 202 height measure. Weight was measured to the nearest 0.1 kg by the Tanita BC-418 MA body composition analyzer· Body mass index (BMI) (calculated as weight (kg) divided by height in meters squared (m^2)). Blood pressure was measured by automatic Omron HEM-7015IT digital blood pressure monitor using an appropriate size cuff, and a sphygmomanometer was used if the automatic device could not be used.

The baseline touch-screen questionnaire was used to assesses other potential confounders, including smoking status (never, past and current), alcohol intake [ethanol intake (g/week) was calculated by the quantity of each type of drink (red wine, white wine, beer/cider, fortified wine, and spirits) multiplied by its standard drink size and reference alcohol content (Alcohol intake (g/week) was calculated by the quantity of each type of drink (red wine, white wine, beer/cider, fortified wine, and spirits) multiplied by its standard drink size and reference alcohol content (1 unit-equivalent described as containing 8g of pure alcohol; 125ml wine=1.6 units-equivalents, 1 pint beer =2.6 units-equivalents, 25ml spirits=1 unit-equivalent, 62.5ml fortified wine=1 unit-equivalent, https://www·drinkaware·co·uk/alcohol-facts/alcoholic-drinks-units/what-is-an-alcohol-unit/)], healthy diet [healthy diet score was evaluated by red meat intake (< median), vegetable intake (≥ median), fruit intake (≥ median), fish intake (≥ median); One point was given for each favorable diet factor and the total diet score ranges from 0 to 4; a healthy diet was defined as a diet score ≥ 2], physical activity (metabolic equivalents minutes per week were calculated according to the International Physical Activity Questionnaire short form: 1 minute walking = 3.3 METS, 1minute moderate physical activity = 4 METS and 1 minute vigorous physical activity = 8 METS).

Townsend deprivation index reflect socioeconomic status, which is a composite measure of deprivation based on unemployment, non-car ownership, non-home ownership and household overcrowding, a higher Townsend index score implies a greater degree of deprivation.

At baseline, the cardiovascular disease was defined by self-reported coronary heart disease and stroke (Field ID 20002 and Field ID 6150); the cancer was defined by any type of self-reported cancer (Field ID 20001 and Field ID 2453). Hypertension was defined as a self-reported history of hypertension or a systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mm Hg or taking antihypertensive medications; High cholesterol was defined as a self-reported history of high cholesterol or taking medications; Osteoarthritis or joint pain was defined as if any type of osteoarthritis or joint pain occurred at any time during the follow-up period (a self-reported history of arthritis or the ICD-10 codes (M15-M19, M255) or the ICD-9 codes (715 and 7194)). Vitamin supplements use was defined as participants who use multivitamin, folic acid, vitamin A, vitamin B, vitamin C, vitamin D or vitamin E· Non-vitamin supplements use was defined as participants who use calcium, iron, zinc, selenium or fish oil.