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学　位　論　文

Studies on association between carbohydrate and fat intake as exposure factors
and the incidence risk of type 2 diabetes

（炭水化物と脂質の摂取に関する曝露因子と糖尿病発症との関連に関する研究）

2024 年 3 月

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List of publications

1. **Akinori Yaegashi**, Takashi Kimura, Takumi Hirata, Hiroyasu Iso, Akiko Tamakoshi. Association between low carbohydrate diet score and incidence of type 2 diabetes among Japanese adults: the JACC Study, Journal of Nutritional Science 12 (2023).
2. **Akinori Yaegashi**, Takashi Kimura, Kenji Wakai, Hiroyasu Iso, Akiko Tamakoshi, Association with total fat and fatty acid intake and incidence risk of type 2 diabetes mellitus among Japanese: JACC Study, Journal of Epidemiology (2024), preprint.
3. **Akinori Yaegashi** and Satoshi Sunohara, Takashi Kimura, Wen Hao, Takato Moriguchi, Akiko Tamakoshi. Association between dietary carbohydrate intake and risk of type 2 diabetes: A systematic review and meta-analysis of cohort studies, Diabetology International 14, 327-338 (2023).

List of presentations at academic conferences

1. **Akinori Yaegashi**, Takashi Kimura, Kenji Wakai, Hiroyasu Iso, Akiko Tamakoshi. Association between low carbohydrate diet score and incidence of type 2 diabetes among Japanese adults: the JACC Study, the 33th Annual Scientific Meeting of the Japan Epidemiological Association, February 1, 2023, Shizuoka, Japan.
2. **Akinori Yaegashi**, Takashi Kimura, Takumi Hirata, Hiroyasu Iso, Akiko Tamakoshi. Association between low carbohydrate diet score and incidence of type 2 diabetes among Japanese adults: The JACC study, IUNS-ICN 22nd International Congress of Nutrition in Tokyo, December 6, 2022, Tokyo, Japan.
3. **Akinori Yaegashi**, Satoshi Sunohara, Takashi Kimura, Wen Hao, Takato Moriguchi, Akiko Tamakoshi. Association between dietary carbohydrate intake and risk of type 2 diabetes: A systematic review and meta-analysis of cohort studies, the 19th Annual Scientific Meeting of the Hokkaido Branch of the Japanese Society of Nutrition and Dietetics, December 4, 2022, Hokkaido, Japan.

Abstract

[Background and purpose] To date, the number of diabetes cases worldwide has steadily increased. Because carbohydrate and fat are one of nutrients affect glucose metabolism, their intakes associated with diabetes risk. As the intake of carbohydrate and fat have changed widely over time, it is important to examine the association between carbohydrate and fat intake as exposure factor and the incidence risk of type 2 diabetes. Therefore, the aim of this study was: (i) to clarify an overview of the association between carbohydrate and fat intakes as exposure factors and incidence of type 2 diabetes (Chapter 1). (ii) to clarify the association between total fat, fatty acids and the incidence of type 2 diabetes among Japanese (Chapter 2). (iii) to clarify the association between low carbohydrate diet score and the incidence of type 2 diabetes among Japanese (Chapter 3).

Chapter 1

[Methods 1] This review was performed in two steps, step 1 and step 2, in that order. Step 1 was conducted to search for the latest systematic review and meta-analysis to investigate the association of carbohydrate and fat intake as exposure factors with the incidence risk of type 2 diabetes using PubMed, and it extracted their data such as exposure factor, the number of studies in all countries and in Asia countries which adopted by the systematic review and meta-analysis, results of meta-analysis comparing highest versus lowest category in all countries and in Asia countries. Step 2 was collected data extraction from the original papers that adopted the systematic reviews and meta-analyses, searched in step 1.

[Results 1] Three papers were extracted, and the exposure factors were carbohydrate, total fat, Saturated fatty acid (SFA), Monounsaturated fatty acid (MUFA), PUFA (Polyunsaturated fatty acid), n-6 PUFA, n-3 PUFA, and “low carbohydrate diet score”. For carbohydrate, the number of studies included in the meta-analysis were 13 (Asia, 6). For fat, the number of studies were 8 (Asia, 2) for total fat, 11 (Asia, 1) for SFA, 9 (Asia, 1) for MUFA, 8 (Asia, 0) for PUFA, 6 (Asia, 1) for n-6 PUFA, and 12 (Asia, 3) for n-3 PUFA. For low carbohydrate diet score, the number of studies were 5 (Asia, 2). These three results of meta-analysis comparing highest versus lowest category found no significant association. For only carbohydrate, subgroup analysis conducted by geographical regions, and differences were observed (Asian: Risk ratio (RR) = 1.29, 95% Confidence interval (CI) 1.15, 1.45; non-Asian: RR = 0.92, 95% CI 0.83, 1.01).

[Discussion 1] This review revealed a shortage of studies in Asia regarding the association of total fat, fatty acids, and “low carbohydrate diet score” with the incidence

risk of type 2 diabetes. Compared to non-Asians, Asians have a higher carbohydrate and lower fat intake in addition to lower insulin secretory capacity. Thus, association of carbohydrate and fat intake with the incidence risk of type 2 diabetes may differ Asians and non-Asians. Therefore, among Asians such as Japanese, further research is needed to investigate the relationship between total fat, fatty acids, and low carbohydrate diet score and type 2 diabetes.

Chapter 2

[Methods 2] This study was conducted using Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC) study data. A total of 19088 Japanese aged 40–79 years were included in this analysis. Dietary assessment was evaluated by a validated food-frequency questionnaire. The incidence of type 2 diabetes was assessed by a self-administered questionnaire about 5 years after baseline. Multivariable logistic regression analysis was used to estimate the OR (Odds ratio) and 95 % CI of incident type 2 diabetes across the quintiles of total fat, SFA, MUFA, PUFA, n-6 PUFA, and n-3 PUFA, with adjustment for potential confounders.

[Results 2] For men, the multivariable-adjusted OR of incident type 2 diabetes for the highest versus lowest quintiles was 0.58 (95% CI, 0.37, 0.90; p-trend = 0.037) for total fat, 0.78 (95% CI, 0.51, 1.21; p-trend = 0.120) for SFA, 0.55 (95% CI, 0.35, 0.86; p-trend = 0.019) for MUFA, 0.61 (95% CI, 0.39, 0.96; p-trend = 0.059) for PUFA, 0.64 (95% CI, 0.42, 0.99; p-trend = 0.111) for n-3 PUFA, and 0.70 (95% CI, 0.45, 1.09; p-trend = 0.115) for n-6 PUFA, indicating that total fat, MUFA, PUFA, and n-3 PUFA were inversely associated with type 2 diabetes. For women, total fat and fatty acids intakes were not significantly associated with type 2 diabetes.

[Discussion 2] The results of this study indicated that total fat, MUFA, PUFA, and n-3 PUFA intakes were inversely associated with type 2 diabetes in Japanese men. In women, total fat and fatty acids intakes were not significantly associated with type 2 diabetes. SFA and n-6 PUFA intakes were not associated with type 2 diabetes in either sex. For total fat, MUFA, PUFA, and n-3 PUFA, although no significant associations with type 2 diabetes were found in the previous meta-analysis, which included many non-Asians, the present study found inverse association with type 2 diabetes in Japanese men. This difference in findings may be due to Asians, such as Japanese, having a lower fat intake than non-Asians.

Chapter 3

[Methods 3] This study was conducted using JACC study data. A total of 19084 Japanese

participants aged 40–79 years were included in this analysis. Dietary assessment was evaluated by a validated food-frequency questionnaire. The overall, animal and vegetable low carbohydrate diet score were calculated by dividing the study participants into eleven categories based on the percentages of energy from carbohydrates, protein and fat. The incidence of type 2 diabetes was assessed by a self-administered questionnaire about 5 years after baseline. Multivariable logistic regression analysis was used to estimate the OR and 95 % CI of incidence type 2 diabetes across the quintiles of each low carbohydrate diet score, with adjustment for potential confounders.
[Results 3] The multivariable-adjusted OR of incidence type 2 diabetes for the highest versus lowest quintiles of the overall and animal low carbohydrate diet score, respectively, were 0.64 (95% CI 0.42, 0.99) and 0.83 (95% CI 0.55, 1.27) for men, 0.78 (95% CI 0.51, 1.18) and 0.84 (95% CI 0.57, 1.24) for women.
[Discussion 3] The present study found that the overall, and animal low carbohydrate diet scores were not associated with the risk of type 2 diabetes in both sexes. The present study did not find any evidence of a link between the higher three low carbohydrate diet scores and a higher risk of type 2 diabetes in both sexes. This contradicts the findings of previous studies in non-Asia. This difference in findings may be due to variations in fish and meat intakes between Asia and non-Asia.

[Conclusions] Based on the review in chapter 1, among Asians such as Japanese, further research is needed to investigate the relationship between total fat, fatty acids, and a low carbohydrate diet score and type 2 diabetes. In chapter 2, among Japanese, higher intakes of total fat, MUFA, PUFA, and n-3 PUFA were inversely associated with type 2 diabetes among Japanese men. In chapter 3, among Japanese, overall, the animal low carbohydrate diet score was not associated with a higher incidence of type 2 diabetes in both sexes.

List of abbreviations

BMI	Body mass index
CI	Confidence interval
FFQ	Food frequency questionnaire
HPFS	Health Professionals Follow-up Study
HR	Hazard ratio
JACC	Japan Collaborative Cohort Study for Evaluation of Cancer Risk
MUFA	Monounsaturated fatty acid
NHS	Nurses' Health Study
OR	Odds ratio
PUFA	Polyunsaturated fatty acid
RR	Risk ratio
SD	Standard deviation
SFA	Saturated fatty acid
US	United States

Overall introduction

Type 2 diabetes is a chronic health condition characterized by high blood glucose levels based on a lack of insulin action, and mechanisms of insufficient insulin action include inadequate insulin supply and decreased insulin sensitivity in the organs where insulin acts (Dietary Reference Intakes for Japanese [2020]). This disease, which is related to metabolism can increase healthcare expenses and the likelihood of developing other medical conditions (Cho et al, 2018), and forced about 1.5 million deaths in 2012 (National Institute for Health and Care Excellence [NICE]; World Health Organization. Global Report on Diabetes. 2016). It is estimated that the number of diabetes cases worldwide will increase by 51% by 2045, reaching 700 million, up from 463 million in 2019 (Saeedi et al, 2019). In the US, the age-adjusted prevalence of diagnosed and undiagnosed diabetes was 9.5% in 1999–2002 and 12.0% in 2013-2016 (National Diabetes Statistics Report, 2020). In Japan, suspected diabetics in 2009 and 2019 were 15.9% and 19.7% in men and 9.4% and 10.8% in women (Ministry of Health, Labor and Welfare of Japan).

The causes of type 2 diabetes are multifactorial and include modifiable factors such as diet and physical activity (Paulweber et al, 2010; Zaccardi et al, 2016). Among dietary factors, macronutrients such as carbohydrate and fat intakes are considered as one of the important factors in the development of diabetes.

Carbohydrate plays an important role as energy sources. Only a small portion of energy from carbohydrates is derived from dietary fiber, most of which is derived from carbohydrates. Carbohydrate produces about 4 kcal/g of energy, and their primary nutritional role is to provide glucose to tissues that normally can only use glucose as an energy source, such as the brain, nervous tissue, red blood cells, renal tubules, testes, and oxygen-deprived skeletal muscle (Dietary Reference Intakes for Japanese [2020]). As carbohydrates are the primary nutrients for post-prandial hyperglycemia and insulin secretion, decreasing their intake can lead to lower insulin demand and increased insulin sensitivity (Bell et al, 2015; Accurso et al, 2008).

Fat is a major component of the cell membrane and a major substrate for energy production. Fatty acids in the absorption of fat-soluble vitamins (A, D, E, and K) and carotenoids. Fatty acids have more than twice the energy value per gram of carbohydrate or protein, suggesting that humans preferentially store fats as energy stores. Fatty acids are classified as SFA, MUFA, and PUFA and it has been reported that different types of fatty acids may affect insulin action. For example, experimental evidence suggests that n-6 PUFA is associated with favorable insulin sensitivity and protects against the development of type 2 diabetes (Maki et al, 2018). The n-3 PUFA modulates insulin sensitivity in phospholipid membranes (Borkman et al, 1993), and MUFA preserves or even enhances β-cell proliferation and has an anti-apoptotic effect (den et al, 2019). In vitro experimental data demonstrated that SFA induces insulin resistance (Boden, 1997).

On the other hand, carbohydrate and fat intakes have changed widely to date. For people over 20 and over in Japan and the US, the energy intake from carbohydrate, total fat, and most fatty acids is shown in Table 1. In Japan, energy intake from carbohydrate is decreasing (Ministry of Health, Labor and Welfare of Japan). Energy intake from total fat, SFA, MUFA, and n-6 PUFA is increasing, and n-3 PUFA intake remains almost unchanged (Ministry of Health, Labor and Welfare of Japan). In addition, in the US, the energy intake from carbohydrate is decreasing. Energy intake from total fat, SFA in women, MUFA in women, and PUFA is increasing, while SFA and MUFA in men are decreasing (National Health and Nutrition Examination Survey).

Table 1. The energy intake from carbohydrate, total fat, and fatty acids in Japan and the US

	Japan (1995)	**Japan (2019)**	**The US (1989–1991)**	**The US (2017–2020)**
Men				
Carbohydrate, % energy	58.6	57.8	46.7	45.0
Total fat, % energy	24.3	27.4	35.0	36.0
Women				
Carbohydrate, % energy	57.0	55.3	49.6	47.0
Total fat, % energy	25.9	29.2	33.9	37.0
	Japan (2005)	**Japan (2019)**	**The US (1989–1991)**	**The US (2017–2020)**
Men				
SFA, % energy	7.2	8.0	12.2	12.0
MUFA, % energy	7.9	10.4	13.2	12.0
PUFA, % energy	Not reported	Not reported	6.9	8.0
n-6 PUFA, % energy	4.4	4.9	Not reported	Not reported
n-3 PUFA, % energy	1.2	1.1	Not reported	Not reported
Women				
SFA, % energy	7.9	8.8	11.7	12.0
MUFA, % energy	8.4	10.8	12.4	13.0
PUFA, % energy	Not reported	Not reported	7.1	9.0
n-6 PUFA, % energy	4.6	5.2	Not reported	Not reported
n-3 PUFA, % energy	1.2	1.2	Not reported	Not reported

Thus, as the intake of carbohydrates and fat, which affect glucose metabolism, have changed widely over time, it is important to examine the association between carbohydrate and fat intake as exposure factors and the incidence of type 2 diabetes.

Therefore, the aim of this study was: (i) to clarify an overview of the association between carbohydrate and fat intakes as exposure factors and incidence of type 2 diabetes: (Chapter 1). (ii) to clarify the association between total fat, fatty acids and the incidence of type 2 diabetes among Japanese (Chapter 2). (iii) to clarify the association between low carbohydrate diet score and the incidence of type 2 diabetes among Japanese (Chapter 3).

Chapter 1: Association of carbohydrate and fat intake as exposure factors with the incidence risk of type 2 diabetes: A review

1.1. Introduction

Many cohort studies reported an association of carbohydrate and fat intakes as exposure factors with diabetes.

For carbohydrate, some studies reported positive association with diabetes (Villegas et al, 2007; Ha et al, 2019), while others reported no association (Sakurai et al, 2016; AlEssa et al, 2015) or negative association (Similä et al, 2012). For fat, some studies found positive association with diabetes (Total fat: Guasch-Ferre et al, 2017, MUFA: Alhazmi et al, 2014; n-6 PUFA and n-3 PUFA: Alhazmi et al, 2014), while others found no association (Total fat and SFA: Alhazmi et al, 2014; n-6 PUFA: Brostow et al, 2011; MUFA: Dow et al, 2016) or negative association (SFA: Kroger et al, 2011; n-3 PUFA: Brostow et al, 2011). For low carbohydrate diet score calculated from carbohydrate, protein, and fat, some studies indicated positive association with diabetes (Bao et al, 2016; de et al, 2011; Sali et al, 2020), while others not (Halton et al, 2008; men: Nanri et al, 2015), or negative association (Women: Nanri et al, 2015).

Thus, to date, the results of the association between carbohydrate and fat as exposure factors and the incidence of type 2 diabetes were inconsistent. These discrepancies may be due to differences in the amount of carbohydrate and fat intakes. For example, Asians have a higher carbohydrate, and a lower fat intake compared to non-Asians (Dehghan et al, 2017; Zhou et al, 2003). In addition, Asians have lower insulin secretory capacity compared to non-Asians (Kadowaki et al, 1984). To clarify these discrepancies, it is necessary to collect previous systematic reviews and meta-analysises, and check the results of their sub-analyses by region, etc. and the information on accepted papers.

Therefore, in this chapter, the aim was to clarify an overview of the association between carbohydrate and fat intake as exposure factors and the incidence of type 2 diabetes to date.

1.2. Method

This review was performed in the order of step 1 and step 2.

1.2.1. Step 1

Step 1 was conducted to collect for the systematic review and meta-analysis published in English to investigate the association of carbohydrate and fat intake as exposure factors with the incidence risk of type 2 diabetes. If multiple studies were found for one factor, the most recent study was extracted. The search was used the PubMed database. The following search was performed: (“diet, carbohydrate restricted”[MeSH Terms] OR “carbohydrate”[Title/Abstract] OR “carbohydrates”[Title/Abstract] OR “Diet, High-Fat”[MeSH Terms] OR “Diet, Fat-Restricted”[MeSH Terms] OR “fat”[Title/Abstract] OR “fats”[Title/Abstract]) AND (“Diabetes Mellitus”[MeSH Terms] OR “diabetes”[Title/Abstract] OR “diabetic”[Title/Abstract] OR “NIDDM”[Title/Abstract] OR “type 2 DM”[Title/Abstract]).

From the systematic review and meta-analysis studies adopted by this process, their data such as author, year of publication, exposure factor, the number of studies in all countries and Asia countries, and results of meta-analysis comparing highest versus lowest category in all countries and in Asia countries were extracted.

1.2.2. Step 2

Step 2 was collected the original papers that adopted in systematic review and meta-analysis, which was searched in step 1. Next, these original papers were extracted their data such as author, publish year, country, follow-up, sample size (n), women (%), BMI (kg/m^2), age, incident diabetes, diabetes assessment method, dietary assessment, exposure category, RR/HR/OR (95% CI), and adjustment factors.

1.3. Results

1.3.1. Characteristics of the studies (Step 1)

In step 1, three systematic review and meta-analysis studies were extracted. The exposure factors were carbohydrate, total fat, SFA, MUFA, PUFA, n-6 PUFA, n-3 PUFA, and overall low carbohydrate diet score (Yaegashi and Sunohara et al, 2023; Hosseini et al, 2022; Neuenschwander et al, 2020). The number of studies included in the systematic review and meta-analysis and results were shown in Table 2.

Table 2. Descritive systematic review and meta-analysis studies of association of carbohydrate and fat intake as exposure factors with incidence risk of type 2 diabetes

Author (publish year)	Search term	Exposure factor	The number of studies included in the systematic review and meta-analysis		Results of meta-analysis comparing highest versus lowest category	
			All countries	Asia countries	All countries	Asia countries
Yaegashi and Sunohara et al (2023)	Earlier than November 18, 2021	Carbohydrate	13	6	1.07 (0.94, 1.21)	1.29 (1.15, 1.45)
Neuenschwander et al (2020)	Earlier than October 28, 2019	Total fat	8	2	1.00 (0.96, 1.05)	Not reported
		SFA	11	1	0.97 (0.92, 1.02)	Not reported
		MUFA	10	1	1.03 (0.99, 1.08)	Not reported
		PUFA	8	0	1.03 (0.89, 1.20)	Not reported
		n-6 PUFA	6	1	0.99 (0.98, 1.00)	Not reported
		n-3 PUFA	12	3	1.03 (0.98, 1.08)	Not reported
Hosseini et al (2022)	Earlier than April 1, 2021	Overall low carbohydrate diet score	5	2	1.14 (0.89, 1.47)	Not reported

For carbohydrate, the number of studies was 13 (Asia, 6) (AlEssa et al, 2015; Alhazmi et al, 2014; Ha et al, 2019; Kim et al, 2020; Meyer et al, 2001; Nanri et al, 2015; Sakurai et al, 2016; Schulze et al, 2008; Similä et al, 2012; Villegas et al, 2007). In systematic review and meta-analysis in all studies, results of meta-analysis comparing highest versus lowest category did not show significant association (Yaegashi and Sunohara et al, 2023). When subgroup analysis was conducted by different geographical regions (Asia and non-Asia), differences were observed (Asian: RR = 1.29, 95% CI 1.15, 1.45, P = 0.59, I^2= 0.0%; non-Asian: RR = 0.92, 95% CI 0.83, 1.01, P = 0.49, I^2 = 21.9%) (Figure 1) (Yaegashi and Sunohara et al, 2023).

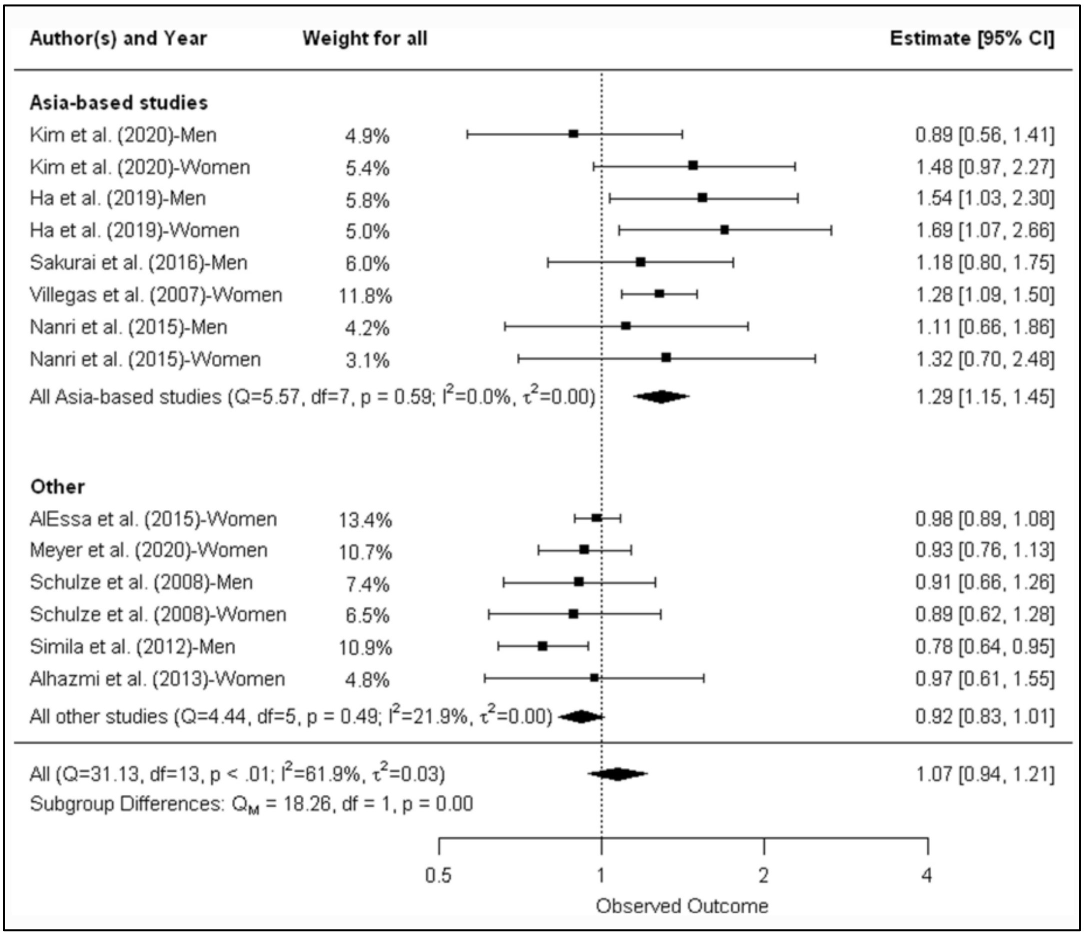

Figure 1. Forest plot indicating the association between carbohydrate intake and type 2 diabetes risk (Yaegashi and Sunohara et al, 2023)

For fat, the number of studies was 8 (Asia, 2) for total fat (Alhazmi et al, 2014; Ericson et al, 2015; Guasch-Ferre et al, 2017; Ha et al, 2019; Lindstrom et al, 2006; Meyer et al, 2001; Salmeron et al, 2001; van et al, 2002; Nanri et al, 2015), 11 (Asia, 1) for SFA (Alhazmi et al, 2014; Dow et al, 2016; Ericson et al, 2015; Guasch-Ferre et al, 2017;

Kroger et al, 2011; Lindstrom et al, 2006; Meyer et al, 2001; Salmeron et al, 1997; Salmeron et al, 2001; Song et al, 2004; van et al, 2002), 9 (Asia, 1) for MUFA (Alhazmi et al, 2014; Dow et al, 2016; Ericson et al, 2015; Guasch-Ferre et al, 2017; Kroger et al, 2011; Meyer et al, 2001; Salmeron et al, 1997; Salmeron et al, 2001; Song et al, 2004), 8 (Asia, 0) for PUFA (Alhazmi et al, 2014; Dow et al, 2016; Ericson et al, 2015; Guasch-Ferre et al, 2017; Kroger et al, 2011; Meyer et al, 2001; Salmeron et al, 1997; Salmeron et al, 2001), 6 (Asia, 1) for n-6 PUFA (Alhazmi et al, 2014; Brostow et al, 2011; Dow et al, 2016; Ericson et al, 2015; Song et al, 2004; Zong et al, 2019), 12 (Asia, 3) for n-3 PUFA (Alhazmi et al, 2014; Brostow et al, 2011; Dow et al, 2016; Ericson et al, 2015; Kaushik et al, 2009; Kroger et al, 2011; Meyer et al, 2001; Song et al, 2004; van et al, 2002; van et al, 2009; Villegas et al, 2011; Zheng et al, 2019). In meta-analysis, all results comparing highest versus lowest category did not show significant association (Neuenschwander et al, 2020). Subgroup analysis was not conducted by different geographical regions (Asia and non-Asia).

For low carbohydrate diet score, the number of studies was 5 (Asia, 2) (Bao et al, 2016; de et al, 2011; Halton et al, 2008; Nanri et al, 2015; Sali et al, 2020). In systematic review and meta-analysis in all studies, results of meta-analysis comparing highest versus lowest category were not significant association (Hosseini et al, 2022). Subgroup analysis was not conducted by different geographical regions (Asia and non-Asia).

1.3.2. Characteristics of the studies (Step 2)

In step 2, the characteristics of the studies that had been adopted in each systematic review and meta-analysis are listed in Table 3-5 (Table 3: Carbohydrate; Table 4: Total fat and fatty acids; Table 5: Low carbohydrate diet score). For n-3 PUFA, two studies in Asia (Brostow et al, 2011; Villegas et al, 2011) showed a negative association with the risk of incidence of diabetes, but four studies in non-Asia (Alhazmi et al, 2014; Dow et al, 2016; Kaushik et al, 2009; Meyer et al, 2001) showed a positive association. For overall and animal low carbohydrate score, one study in Japan (Nanri et al, 2015) showed a negative association with the risk of incidence of diabetes, but three studies in the US and Iran (Sali et al, 2020; Bao et al, 2016; de et al, 2011) showed a positive association. For the common characteristics of the three exposure factors, several non-Asian studies reported long follow-up periods, larger numbers of participants, and repeated FFQ (Kaushik et al, 2009; Halton et al. Van et al, 2002, Bao et al, 2016, de et al, 2011; Salmerón et al, 2001; AlEssa et al, 2015), but all Asian studies reported no such studies.

Table 3. Characteristics of the studies included in the systematic-review and meta-analysis for association carbohydrate with the incidence risk of type 2 diabetes

Author, (publish year), country	Follow-up	Sample size, n	Women (%)	Mean BMI (kg/m^2)[a]	Mean age (age range)	Incident diabetes, n (%)	Diabetes Assessment method	Dietary Assessment	Carbohydrate-intake category[c,d]	RR/HR/OR (95% CI)	Adjustment factors
Kim et al. (2020), Korea, men	3.96 years	3032	64	23.8	62.2	130 (4.3)	Self-reported and medical records	Validated FFQ	T1: 298 g/d (168.9, 316) T2: 327.6 g/d (316.1, 336.2) T3: 346.2 g/d (336.2, 389.6)	T1: 1.00 (reference) T2: 1.23 (0.81, 1.86) T3: 0.89 (0.56, 1.40)	Age, smoking status, alcohol consumption, BMI, physical activity level, education, calcium intake
Kim et al. (2020), Korea, women		5278		24.4	60.9	192 (3.6)			T1: 269.9 g/d (156.4–285.9) T2: 297.0 g/d (286.0–306.3) T3: 314.8 g/d (306.3–351.1)	T1: 1.00 (reference) T2: 1.14 (0.76, 1.73) T3: 1.48 (0.97, 2.28)	
Ha et al. (2019), Korea, men	11.5 years	2684	52	Q1: 24.4 Q4: 23.6	(40–69)	533 (19.9)	Medical records	Validated FFQ	Q1: 64.7% (46.7, 67.7) Q2: 69.8% (67.7, 71.7) Q3: 73.7% (71.7, 75.6) Q4: 78.0% (75.6, 88.2)	Q1: 1.00 (reference) Q2: 0.92 (0.69, 1.112) Q3: 1.40 (1.02, 1.93) Q4: 1.54 (1.03, 2.30)	Age, family history of diabetes, smoking status, alcohol consumption, BMI, physical activity level, education, income level, marital status, residence, protein intake, total energy intake, fasting blood glucose
Ha et al. (2019), Korea, women		2911	52	Q1: 24.3 Q4: 24.6		477 (16.4)			Q1: 66.3% (37.9, 69.9) Q2: 71.8% (69.6, 73.7) Q3: 75.6% (73.7, 77.6) Q4: 80.4% (77.6, 88.6)	Q1: 1.00 (reference) Q2: 1.11 (0.82, 1.51) Q3: 1.09 (0.75, 1.57) Q4: 1.69 (1.08, 2.67)	
Sakurai et al. (2016), Japan	10 years	2006	0	23.4	45.9	232 (11.6)	Medical records	Validated FFQ	[f]Q1: (< 50.0%) Q2: (50.0–57.4%) Q3: (57.5–65.0%) Q4: (> 65.0%) [g] Q1: (< 285.7 g/d) Q2: (285.8, 313.8 g/d) Q3: (313.9, 341.7 g/d) Q4: (≥ 341.8 g/d)	[f]Q1: 0.88 (0.58, 1.31) Q2: 1.00 (reference) Q3: 0.87 (0.61, 1.23) Q4: 1.18 (0.80, 1.76) [g] Q1: 0.95 (0.64, 1.41) Q2: 1.00 (reference) Q3: 0.96 (0.65, 1.42) Q4: 1.19 (0.80, 1.76)	Age, family history of diabetes, smoking status, alcohol consumption, physical activity level, occupation type, total energy intake, total fiber intake, fasting plasma glucose level
AlEssa et al. (2015), the US	24 years	70025	100	Q1: 25.1 Q3: 24.9 Q5: 24.3	(30–55)	6934 (9.9)	Self-reported	Validated FFQ	Q1: 159 g/d Q2: 181.0 g/d Q3: 195 g/d Q4: 208.3 g/d Q5: 228.4 g/d	Q1: 1.00 (reference) Q2: 0.96 (0.89, 1.04) Q3: 0.96 (0.89, 1.04) Q4: 0.99 (0.91, 1.08) Q5: 0.98 (0.89, 1.08)	Age, BMI, family history of diabetes, postmenopausal status, smoking status, alcohol intake, physical activity level, multivitamin use, race, total energy intake, red meat consumption, coffee consumption, magnesium intake, ratio of polyunsaturated fat to saturated fat, trans-fat intake (all dietary variables in quintiles)

Meyer et al. (2000), the US	6 years	35988	100	Q1: 26.9 Q2: 26.8 Q3: 26.8 Q4: 26.6 Q5: 26.8	(55–69)	1141 (3.2)	Self-reported	Validated FFQ	Q1: 176 g/d (< 192.1) Q2: 202 g/d (192.1–210.6) Q3: 218 g/d (210.7–225.6) Q4: 234 g/d (225.7–243.8) Q5: 259 g/d (> 243.8)	Q1: 1.00 (reference) Q2: 1.05 (0.87, 1.26) Q3: 0.98 (0.81, 1.19) Q4: 0.90 (0.74, 1.09) Q5: 0.93 (0.76, 1.13)	Age, total energy intake, BMI, waist-to-hip ratio, education level, pack-years of smoking, alcohol intake, physical activity level
Villegas et al. (2007), China	4.6 years	64227	100	Not reported	(40–70)	1608 (2.5)	Self-reported	Validated FFQ	Q1: 263.5 g/d[e] Q2: 269.1 g/d Q3: 276.3 g/d Q4: 287.1 g/d Q5: 337.6 g/d	Q1: 1.00 (reference) Q2: 0.96 (0.80, 1.15) Q3: 0.87 (0.73, 1.05) Q4: 1.09 (0.92, 1.29) Q5: 1.28 (1.09, 1.50)	Age, history of hypertension, smoking status, alcohol consumption, physical activity level, BMI, waist-hip ratio, education level, occupation type, income, total energy intake
Schulze et al. (2008), Germany, men	7–11 years	9702	61	Q1: 27.2 Q2: 26.9 Q3: 26.7 Q4: 26.8 Q5: 26.7	(35–65)	844 (3.4)	Self-reported	Validated FFQ	Q1: 30.9% Q2: 35.2% Q3: 38.3% Q4: 41.5% Q5: 46.4%	Q1: 1.00 (reference) Q2: 0.83 (0.62, 1.10) Q3: 0.92 (0.69, 1.23) Q4: 0.92 (0.68, 1.25) Q5: 0.91 (0.66, 1.26)	Age, education level, occupational activity, engagement in sport, smoking, alcohol intake, total energy intake
Schulze et al. (2008), Germany, women		15365		Q1: 25.8 Q2: 25.5 Q3: 25.6 Q4: 25.6 Q5: 25.7					Q1: 36.7% Q2: 41.2% Q3: 44.1% Q4: 47.0% Q5: 51.4%	Q1: 1.00 (reference) Q2: 0.90 (0.64, 1.27) Q3: 0.97 (0.69, 1.36) Q4: 0.95 (0.66, 1.35) Q5: 0.89 (0.62, 1.29)	
Similä et al. (2012), Finland	12 years	Men 25943	0	Median Q1: 26.1 Q2: 26.0 Q3: 25.9 Q4: 25.7 Q5: 25.7	(50–69)	1098 (4.2)	Self-reported	Validated FFQ	Q1: 33.4% Q2: 37.5% Q3: 40.4% Q4: 43.3% Q5: 47.4%	Q1: 1.00 (reference) Q2: 0.77 (0.65, 0.92) Q3: 0.81 (0.68, 0.97) Q4: 0.81 (0.68, 0.98) Q5: 0.78 (0.64, 0.94)	Age, intervention group, BMI, smoking status, physical activity level, total energy intake, coffee consumption
Alhazmi et al. (2014), Australia	6 years	Women 8370	100	Not reported	(45–50)	311 (3.7)	Self-reported	Validated FFQ	Q1: 104.38 g/d Q2: 139.28 g/d Q3: 166.76 g/d Q4: 198.65 g/d Q5: 256.91 g/d	Q1: 1.00 (reference) Q2: 1.03 (0.70, 1.50) Q3: 1.04 (0.71, 1.54) Q4: 0.85 (0.55, 1.30) Q5: 0.97 (0.61, 1.55)	Area of residence, education level, current smoking status, physical activity level, good self-rated health, menopausal status, BMI, alcohol consumption, total energy intake, saturated fatty acid intake, mono-unsaturated fatty acid intake

Nanri et al. (2015), Japan, men	5 years	27799	57	23.6	(40–69)	1191 (1.8)	Self-reported	Validated FFQ	Q1: 40.2% (8.9, 44.8) Q2: 48.0% (44.8, 50.7) Q3: 53.1% (50.7, 55.5) Q4: 58.2% (55.5, 61.1) Q5: 65.3% (61.1, 87.6)	Q1: 1.00 (reference) Q2: 1.24 (0.93, 1.64) Q3: 1.18 (0.84, 1.65) Q4: 1.18 (0.79, 1.76) Q5: 1.11 (0.66, 1.86)	Age, family history of diabetes, history of hypertension, smoking status, alcohol consumption, BMI, physical activity, study area, total energy intake, coffee consumption, magnesium intake, calcium intake, vitamin D intake, fat intake
Nanri et al. (2015), Japan, women		36875							Q1: 45.0% (5.5, 49.1) Q2: 51.9% (49.1, 54.1) Q3: 56.1% (54.1, 58.1) Q4: 60.3% (58.1, 62.9) Q5: 66.5% (62.9, 88.5)	Q1: 1.00 (reference) Q2: 1.15 (0.80, 1.66) Q3: 1.19 (0.78, 1.81) Q4: 1.30 (0.80, 2.12) Q5: 1.32 (0.70, 2.48)	

[a] Values are presented as means ± standard deviations. If the subjects' full values were not reported in the paper, the values were determined based on dietary carbohydrate intake. Meyer et al study was determined based on a whole grain intake

[b] Values are presented as means ± standard deviations (range). The range is enclosed in parentheses ().

[c] Units of % indicate a value adjusted for energy using the density method; units of g/d indicate a value adjusted for energy using the residual method. If the energy-adjusted values were obtained using both the density and residue methods, both are shown.

[d] Values are medians and (ranges). The range is enclosed in parentheses ().

[e] Values are amounts divided according to the glycemic index.

[f] Values are amounts divided according to energy-adjusted carbohydrates using the density method.

[g] Values are amounts divided according to energy-adjusted carbohydrates using the residual method

Table 4. Characteristics of the studies included in the systematic review and meta-analysis for association total fat and fatty acids with incidence risk of type 2 diabetes

Author, (publish year*), country	Follow-up	Sample size, n	Women (%)	Mean BMI (kg/m^2)*[1]	Mean age (age range)	Carbohydrate (% of energy)*[1]	Fat (% of energy)*[1]	Incident diabetes, n (%)	Diabetes Assessment method	Dietary Assessment	Exposure	Exposure categories	OR/RR/HR (95% CI)	Adjustment factors
Alhazmi et al. (2014), Australia	6 years	8370	100	Not reported	(45-50)	Not reported	Not reported	311 (3.7)	Self-reported	Validated FFQ	Total fat	Q1: 33.87 g/d Q2: 47.47 g/d Q3: 58.99 g/d Q4: 71.93 g/d Q5: 95.51 g/d	Q1: 1.00 (reference) Q2: 1.21 (0.81, 1.82) Q3: 1.12 (0.74, 1.69) Q4: 1.33 (0.88, 2.02) Q5: 1.27 (0.84, 1.91)	Area of residence, education, current smoking status, physical activity, self-rated health as good, menopausal status, BMI, alcohol consumption, total energy intake (kJ/d), SFA and MUFA intakes for total carbohydrate, SFA, MUFA and fibre intakes for total protein, and fibre intake for total fat
											SFA	Q1: 12.37 g/d Q2: 17.95 g/d Q3: 22.81 g/d Q4: 29.01 g/d Q5: 40.01 g/d	Q1: 1.00 (reference) Q2: 1.15 (0.79, 1.68) Q3: 1.22 (0.84, 1.76) Q4: 0.98 (0.67, 1.43) Q5: 0.71 (0.47, 1.07)	
											MUFA	Q1: 11.69 g/d Q2: 16.43 g/d Q3: 20.58 g/d Q4: 25.32 g/d Q5: 34.32 g/d	Q1: 1.00 (reference) Q2: 1.29 (0.85, 1.94) Q3: 1.18 (0.76, 1.84) Q4: 1.30 (0.83, 2.02) Q5: 1.64 (1.06, 2.54)	
											PUFA	Q1: 4.31 g/d Q2: 6.77 g/d Q3: 9.15 g/d Q4: 11.95 g/d Q5: 16.52 g/d	Q1: 1.00 (reference) Q2: 0.81 (0.53, 1.25) Q3: 1.10 (0.73, 1.67) Q4: 1.07 (0.71, 1.61) Q5: 1.27 (0.84, 1.90)	
											Total omega-3	Q1: 0.61 g/d Q2: 0.86 g/d Q3: 1.08 g/d Q4: 1.37 g/d Q5: 1.97 g/d	Q1: 1.00 (reference) Q2: 0.98 (0.63, 1.52) Q3: 1.27 (0.84, 1.92) Q4: 1.44 (0.97, 2.16) Q5: 1.55 (1.03, 2.32)	
											Total omega-6	Q1: 3.54 g/d Q2: 5.47 g/d Q3: 7.43 g/d Q4: 9.86 g/d Q5: 13.87 g/d	Q1: 1.00 (reference) Q2: 1.25 (0.83, 1.90) Q3: 1.18 (0.76, 1.83) Q4: 1.28 (0.82, 1.99) Q5: 1.60 (1.03, 2.48)	

Brostow et al. (2011), China	5.7 years	43176	57.2[*4]	Q1 23.0 Q3 23.0 Q5 23.1 (Values divided into 5 groups by total omega-3)	(45-74)	Not reported	Not reported	2252 (5.2)	Self-reported	Validated FFQ	Total omega-3	Q1: 0.45 g/d Q2: 0.66 g/d Q3: 0.82 g/d Q4: 1.02 g/d Q5: 1.54 g/d	Q1: 1.00 (reference) Q2: 0.87 (0.75, 1.00) Q3: 0.88 (0.76, 1.02) Q4: 0.80 (0.68, 0.94) Q5: 0.78 (0.65, 0.94)	Age, sex, dialect, year of interview, educational level, BMI, physical activity, smoking status, alcohol use, hypertension, intakes of omega-6 or omega-3, MUFA, SFA, dietary fiber, protein, and total energy
											Total omega-6	Q1: 3.50 g/d Q2: 5.40 g/d Q3: 7.10 g/d Q4: 9.30 g/d Q5: 14.60 g/d	Q1: 1.00 (reference) Q2: 0.94 (0.81, 1.08) Q3: 1.00 (0.87, 1.17) Q4: 0.91 (0.78, 1.07) Q5: 0.93 (0.87, 1.12)	
Dow et al. (2016), France	18 years	71334	100	Not reported	52.9	Not reported	Not reported	2610 (3.7)	Self-report or reimbursements from health insurance records or medical records	Validated FFQ	SFA	T1: <33.3 g/d T2: 33.3-38.9 g/d T3: ≥38.9 g/d	T1: 1.00 (reference) T2: 1.06 (0.95, 1.19) T3: 1.07 (0.92, 1.25)	Daily energy intake, alcohol consumption, level of education, family history of diabetes, physical activity, hypertension, hypercholesterolaemia, smoking status, tertile groups of remaining fatty acid groups and BMI (age as time-scale in cox regression model)
											MUFA	T1: <28.7 g/d T2: 28.7-33.3 g/d T3: ≥33.3 g/d	T1: 1.00 (reference) T2: 1.01 (0.91, 1.12) T3: 1.06 (0.95, 1.19)	
											PUFA	T1: <12.0 g/d T2: 12.0-15.3 g/d T3: ≥15.3 g/d	T1: 1.00 (reference) T2: 1.03 (0.93, 1.14) T3: 1.06 (0.96, 1.17)	
											Total omega-3	T1: <1.3g/d T2: 1.3-1.6 g/d T3: ≥1.6 g/d	T1: 1.00 (reference) T2: 1.10 (0.99, 1.22) T3: 1.26 (1.13, 1.41)	
											Total omega-6	T1: <10.5 g/d T2: 10.5-13.7 g/d T3: ≥13.7 g/d	T1: 1.00 (reference) T2: 1.01 (0.91, 1.12) T3: 1.00 (0.90, 1.10)	

Ericson et al. (2015), Sweden	14 years	26930	61.2	Diabetes group: 28.4 Non diabetes group: 25.4	(45-74)	Diabetes 45.9 Non diabetes 46.3	Diabetes group: 38.3 Non diabetes group: 38.5	2860 (10.6)	via at least one of 7 registries or at new screenings or examinations during follow-up information on date of diagnosis was used from 2 registries (the regional Diabetes 2000 registry of Scania and the Swedish National Diabetes Registry) that required a physician diagnosis according to established diagnosis criteria: fasting plasma glucose concentration ≥7.0 mmol/L or fasting whole blood concentration ≥6.1 mmol/L, measured at 2 different occasions.	Validated FFQ	Total fat	Q1: 31% Q2: 35% Q3: 38% Q4: 41% Q5: 46%	Q1: 1.00 (reference) Q2: 1.00 (0.88, 1.12) Q3: 0.95 (0.85, 1.07) Q4: 0.93 (0.83, 1.05) Q5: 0.96 (0.85, 1.08)	Age, sex, method version, season, total energy intake, leisure-time physical activity, smoking, alcohol intake, education and BMI
											SFA	Q1: 12% Q2: 14% Q3: 16% Q4: 18% Q5: 22%	Q1: 1.00 (reference) Q2: 1.07 (0.96, 1.19) Q3: 0.91 (0.81, 1.02) Q4: 0.93 (0.82, 1.04) Q5: 0.91 (0.81, 1.02)	
											MUFA	Q1: 11 % Q2: 12% Q3: 13% Q4: 14% Q5: 16%	Q1: 1.00 (reference) Q2: 0.99 (0.88, 1.12) Q3: 0.98 (0.87, 1.10) Q4: 1.03 (0.91, 1.16) Q5: 1.01 (0.89, 1.13)	
											PUFA	Q1: 4% Q2: 5% Q3: 6% Q4: 7% Q5: 8%	Q1: 1.00 (reference) Q2: 1.08 (0.96, 1.22) Q3: 1.04 (0.92, 1.17) Q4: 1.08 (0.96, 1.22) Q5: 1.07 (0.95, 1.20)	
											Total omega-3	Q1: 0.7% Q2: 0.8% Q3: 0.9% Q4: 1.1% Q5: 1.4%	Q1: 1.00 (reference) Q2: 0.90 (0.80, 1.02) Q3: 0.91 (0.81, 1.02) Q4: 0.93 (0.83, 1.05) Q5: 1.00 (0.89, 1.12)	
											Long-chain omega-3	Q1: 0.07% Q2: 0.12% Q3: 0.19% Q4: 0.29% Q5: 0.52%	Q1: 1.00 (reference) Q2: 1.01 (0.90, 1.14) Q3: 0.99 (0.88, 1.12) Q4: 0.92 (0.81, 1.04) Q5: 1.07 (0.94, 1.20)	
											Total omega-6	Q1: 3.2% Q2: 4.0% Q3: 4.7% Q4: 5.5% Q5: 6.8%	Q1: 1.00 (reference) Q2: 1.13 (1.00, 1.28) Q3: 1.07 (0.95, 1.21) Q4: 1.11 (0.98, 1.25) Q5: 1.09 (0.97, 1.23)	

Guasch-Ferre et al. (2017), Spain	4.3 years	3349	62.2	30	(55-80)	42.9	38.2	266 (7.9)	Type 2 diabetes incidence diagnosed according to ADA criteria	Validated FFQ	Total fat	Q1: 30.55% Q2: 36.23% Q3: 40.43% Q4: 45.53%	Q1: 1.00 (reference) Q2: 1.06 (0.69, 1.61) Q3: 1.03 (0.67, 1.57) Q4: 1.69 (1.12, 2.54)	Age, sex, intervention group, BMI, smoking status, educational status, leisure-time physical activity, baseline hypertension or use of antihypertensive medication, total energy intake, alcohol intake, quartiles of fiber, protein intake, dietary cholesterol, specific types of fat, hypercholesterolemia or use of lipid-lowering drugs and fasting plasma glucose at baseline
											MUFA	Q1: 14.12% Q2: 17.54% Q3: 20.31% Q4: 23.90%	Q1: 1.00 (reference) Q2: 0.83 (0.55, 1.28) Q3: 0.87 (0.57, 1.33) Q4: 1.10 (0.71, 1.71)	
											PUFA	Q1: 4.14% Q2: 5.20% Q3: 6.23% Q4: 8.28%	Q1: 1.00 (reference) Q2: 1.25 (0.81, 1.91) Q3: 1.32 (0.85, 2.05) Q4: 1.56 (1.03, 2.35)	
											SFA	Q1: 7.29% Q2: 8.92% Q3: 10.31% Q4: 12.21%	Q1: 1.00 (reference) Q2: 1.31 (0.84, 2.06) Q3: 1.21 (0.74, 1.98) Q4: 1.16 (0.67, 1.99)	
Ha et al. (2019), Korea, Men	11.5 years	2684	52	Q1: 23.7 Q4: 24.3 (Values divided into 4 groups by total fat)	(40-69)	Q1: 78.3 Q4: 64.2 (Values divided into 4 groups by total fat)	Q1: 9.9 Q4: 20.6 (Values divided into 4 groups by total fat)	533 (19.9)	According to WHO guidelines: (1) fasting blood glucose level >=126 mg/dl, (2)2-h blood glucose level >=200 mg/dl, (3) physician's diagnosis of diabetes, and (4) treatment with oral hyperglycemic medication or insulin	Validated FFQ	Total fat	Q1: 10.2% Q2: 13.5% Q3: 16.3% Q4: 20.2%	Q1: 1.40 (1.00, 1.96) Q2: 1.22 (0.92, 1.61) Q3: 0.96 (0.74, 1.25) Q4: 1.00 (reference)	Alcohol consumption, BMI, education level, household income level, marital status, smoking status, parental history of diabetes, physical activity, residence, protein intake (% of total energy), total energy intake, fasting blood glucose at baseline
Ha et al. (2019), Korea, women		2911		Q1: 24.6 Q4: 24.3 (Values divided into 4 groups by total fat)		Q1: 80.5 Q4: 65.9 (Values divided into 4 groups by total fat)	Q1: 8.1 Q4: 19.0 (Values divided into 4 groups by total fat)	477 (16.4)				Q1: 8.2% Q2: 11.6% Q3: 14.4% Q4: 18.6%	Q1: 1.74 (1.18, 2.57) Q2: 1.31 (0.95, 1.81) Q3: 1.14 (0.85, 1.53) Q4: 1.00 (reference)	

Kaushik et al. (2009), the US, women, (NHS)	29 years	61031	100	Q1: 24.6 Q3: 24.9 Q5: 24.9 (Values divided into 5 groups by long-chain omega-3)	(30-55)	Not reported	Not reported	4159 (6.8)	Self-report, validated according to the National Diabetes Data Group criteria	Validated repeated FFQ	Long-chain omega-3	Q1: 0.06 g/d Q2: 0.12 g/d Q3: 0.18 g/d Q4: 0.27 g/d Q5: 0.49 g/d	Q1: 1.00 (reference) Q2: 1.00 (0.91, 1.11) Q3: 1.12 (1.02, 1.24) Q4: 1.17 (1.05, 1.29) Q5: 1.23 (1.11, 1.37)	Age, smoking, alcohol consumption, physical activity, family history of diabetes, BMI, intakes of SFA, TFA, ALA, LA, caffeine, cereal fiber, glycemic index, calories, menopausal status and postmenopausal hormone use
Kaushik et al. (2009), the US, Women, (NHS2)	15 years	61669	100	Q1: 24.5 Q3: 24.7 Q5: 24.4 (Values divided into 5 groups by long-chain omega-3)	(26-46)			2728 (4.4)	Self-report, validated according to the National Diabetes Data Group criteria			Q1: 0.06 g/d Q2: 0.10 g/d Q3: 0.15 g/d Q4: 0.22 g/d Q5: 0.36 g/d	Q1: 1.00 (reference) Q2: 1.04 (0.92, 1.17) Q3: 1.08 (0.95, 1.22) Q4: 1.15 (1.02, 1.30) Q5: 1.25 (1.10, 1.42)	
Kaushik et al. (2009), the US, Men (HPFS)	18 years	42504	0	Q1: 24.9 Q3: 24.9 Q5: 24.7 (Values divided into 5 groups by long-chain omega-3)	(39-78)	Not reported	Not reported	2493 (5.9)	Self-report, validated according to the National Diabetes Data Group criteria	Validated repeated FFQ	Long-chain omega-3	Q1: 0.09 g/d Q2: 0.18 g/d Q3: 0.28 g/d Q4: 0.39 g/d Q5: 0.62 g/d	Q1: 1.00 (reference) Q2: 1.00 (0.88, 1.13) Q3: 0.99 (0.87, 1.12) Q4: 1.11 (0.98, 1.26) Q5: 1.12 (0.98, 1.28)	Age, smoking, alcohol consumption, physical activity, family history of diabetes, BMI, intakes of SFA, TFA, ALA, LA, caffeine, cereal fiber, glycemic index and calories
Kroger et al. (2011), Germany	7 years	2724	55.4	Sub cohort group: 25.9 Cases group: 30.4	(35-65)	Sub cohort group: 41.9 Cases group: 40.6	Sub cohort group: 39.3 Cases group: 40.1	673 (24.7)	The prevalence of diabetes at baseline was evaluated by a physician who used information on self-reported medical diagnoses, medication records, and dieting behavior. Uncertainties regarding a proper diagnosis at baseline were clarified with the participant or treating physician.	Validated FFQ	SFA	Q1: 36.1% of total fat intake Q2: 39.1% of total fat intake Q3: 41.1% of total fat intake Q4: 43.5% of total fat intake Q5: 47.0% of total fat intake	Q1: 1.00 (reference) Q2: 0.71 (0.51, 1.00) Q3: 0.86 (0.63, 1.18) Q4: 0.73 (0.52, 1.02) Q5: 0.71 (0.50, 0.99)	Age, sex, BMI, waist circumference, cycling, sports activity, education, smoking status, alcohol intake, occupational activity, coffee intake (energy adjusted), fiber intake (energy adjusted), total fat intake, and total energy intake
											MUFA	Q1: 31.8% of total fat intake Q2: 33.0% of total fat intake Q3: 33.8% of total fat intake Q4: 34.7% of total fat intake Q5: 36.1% of total fat intake	Q1: 1.00 (reference) Q2: 0.80 (0.57, 1.13) Q3: 1.05 (0.75, 1.46) Q4: 0.79 (0.56, 1.12) Q5: 0.98 (0.71, 1.35)	
											PUFA	Q1: 11.6% of total fat intake Q2: 14.8% of total fat intake Q3: 17.5% of total fat intake Q4: 20.2% of total fat intake Q5: 24.5% of total fat intake	Q1: 1.00 (reference) Q2: 1.01 (0.71, 1.43) Q3: 1.30 (0.91, 1.86) Q4: 1.21 (0.86, 1.72) Q5: 1.26 (0.89, 1.77)	
											Long-chain omega-3	Q1: 0.04% of total fat intake Q2: 0.16% of total fat intake Q3: 0.23% of total fat intake Q4: 0.32% of total fat intake Q5: 0.59% of total fat intake	Q1: 1.00 (reference) Q2: 1.01 (0.71, 1.46) Q3: 0.82 (0.58, 1.18) Q4: 0.97 (0.69, 1.36) Q5: 1.29 (0.95, 1.75)	

Lindstrom et al. (2006), Finland	4.1 years	500	66.8	31	55	No diabetes group: 44 Diabetes group: 42	No diabetes group: 36 Diabetes group: 37	114 (22.8)	Diabetes was defined according to the WHO 1985 criteria	3-day food record at baseline and before every annual study visit	Total fat	Q1: <30% Q2: 30-33.16% Q3: 33.16-36.86% Q4: >36.86%	Q1: 1.00 (reference) Q2: 1.07 (0.53, 2.15) Q3: 1.40 (0.74, 2.64) Q4: 2.14 (1.16, 3.92)	Intervention assignment, sex, age, baseline weight, baseline 2-h glucose, physical activity at baseline and during follow-up period, baseline intake of explanatory nutrient, weight change
											SFA	Q1: <12.14% Q2: 12.14-14.4% Q3: 14.4-16.63% Q4: >16.63%	Q1: 1.00 (reference) Q2: 1.15 (0.58, 2.29) Q3: 1.99 (1.09, 3.64) Q4: 1.73 (0.89, 3.38)	
Meyer et al. (2001), the US	11 years	35988	100	Q1: 26.2 Q5: 27.2 (Values divided into 5 groups by total fat)	(55-69)	Not reported	Not reported	1890 (5.3)	Self-report, with validation of 85 cohort participants in 1988	Validated FFQ	Total fat	Q1: 55.7 g/d Q2: 56.1 g/d Q3: 60.1 g/d Q4: 66.8 g/d Q5: 86.6 g/d	Q1: 1.00 (reference) Q2: 1.00 (0.85, 1.17) Q3: 0.95 (0.81, 1.11) Q4: 0.93 (0.79, 1.10) Q5: 0.89 (0.75, 1.05)	Age, total energy, WHR, BMI, physical activity, cigarette smoking, alcohol consumption, education, marital status, residential area, hormone replacement therapy, dietary magnesium and cereal fiber
											SFA	Q1: 19.3 g/d Q2: 19.2 g/d Q3: 20.4 g/d Q4: 23.2 g/d Q5: 31.8 g/d	Q1: 1.00 (reference) Q2: 1.05 (0.89, 1.24) Q3: 1.06 (0.90, 1.25) Q4: 1.10 (0.94, 1.29) Q5: 1.00 (0.85, 1.18)	
											PUFA	Q1: 8.9 g/d Q2: 9.2 g/d Q3: 10.4 g/d Q4: 12.2 g/d Q5: 16.6 g/d	Q1: 1.00 (reference) Q2: 0.94 (0.81, 1.08) Q3: 0.91 (0.78, 1.06) Q4: 0.85 (0.73, 0.99) Q5: 0.88 (0.76, 1.02)	
											MUFA	Q1: 20.4 g/d Q2: 20.9 g/d Q3: 22.7 g/d Q4: 25.7 g/d Q5: 33.8 g/d	Q1: 1.00 (reference) Q2: 0.99 (0.84, 1.16) Q3: 1.01 (0.86, 1.19) Q4: 0.90 (0.76, 1.06) Q5: 0.96 (0.82, 1.13)	
											Long-chain omega-3	Q1: 0.03 g/d Q2: 0.09 g/d Q3: 0.13 g/d Q4: 0.20 g/d Q5: 0.39 g/d	Q1: 1.00 (reference) Q2: 0.98 (0.84, 1.14) Q3: 1.01 (0.87, 1.18) Q4: 0.99 (0.85, 1.15) Q5: 1.20 (1.03, 1.39)	

Salmeron et al. (1997), the US	6 years	42759	0	Q1: 25.7 Q2: 25.5 Q3: 25.5 Q4: 25.4 Q5: 25.3 (Values divided into 5 groups by Glycemic index)	(40-75)	Not reported	Not reported	523 (1.2)	According the criteria of NIDDM proposed by the National Diabetes Data Group (1979) and the World Health Organization (1985)	Validated FFQ	SFA	Q1: 16.7 g/d Q2: 21.3 g/d Q3: 24.3 g/d Q4: 27.3 g/d Q5: 32.1 g/d	Q1: 1.00 (reference) Q2: 1.20 (0.87, 1.65) Q3: 1.31 (0.96, 1.78) Q4: 1.17 (0.85, 1.59) Q5: 1.03 (0.75, 1.41)	Age, BMI, alcohol intake, smoking status, physical activity and family history of diabetes
											PUFA	Q1: 9.2 g/d Q2: 11.3 g/d Q3: 12.8 g/d Q4: 14.5 g/d Q5: 17.4 g/d	Q1: 1.00 (reference) Q2: 1.00 (0.76, 1.34) Q3: 1.00 (0.76, 1.34) Q4: 1.16 (0.89, 1.54) Q5: 1.01 (0.77, 1.35)	
											MUFA	Q1: 19.5 g/d Q2: 24.2 g/d Q3: 27.3 g/d Q4: 30.2 g/d Q5: 36.6 g/d	Q1: 1.00 (reference) Q2: 1.04 (0.76, 1.42) Q3: 1.26 (0.93, 1.69) Q4: 1.16 (0.85, 1.56) Q5: 1.01 (0.74, 1.37)	
Salmeron et al. (2001), the US	14 years	84204	100	Q1: 24 Q3: 24 Q5: 24 (Values divided into 5 groups by PUFA)	(30-55)	Not reported	Not reported	2507 (3.0)	According the criteria of NIDDM proposed by the National Diabetes Data Group (1979) and the World Health Organization (1985)	Validated FFQ	Total fat	Q1: 28.9% Q2: 33.9% Q3: 37.2% Q4: 40.6% Q5: 46.1%	Q1: 1.00 (reference) Q3: 0.87 (0.77, 1.00) Q3: 1.01 (0.88, 1.15) Q4: 0.97 (0.85, 1.10) Q5: 0.97 (0.85, 1.11)	Age, time period, BMI, cigarette smoking, parental history of diabetes, alcohol consumption, physical activity, percentage of energy from protein, total energy intake and dietary cholesterol
											SFA	Q1: 10.7% Q2: 12.8% Q3: 14.3% Q4: 16.0% Q5: 18.8%	Q1: 1.00 (reference) Q2: 0.97 (0.83, 1.12) Q3: 0.96 (0.81, 1.14) Q4: 1.03 (0.86, 1.24) Q5: 0.99 (0.80, 1.21)	
											MUFA	Q1: 10.9% Q2: 13.1% Q3: 14.6% Q4: 16.3% Q5: 19.3%	Q1: 1.00 (reference) Q2: 1.07 (0.91, 1.25) Q3: 1.05 (0.88, 1.26) Q4: 1.02 (0.83, 1.25) Q5: 1.06 (0.84, 1.33)	
											PUFA	Q1: 2.9 % Q2: 3.4% Q3: 4.1% Q4: 4.8% Q5: 6.2%	Q1: 1.00 (reference) Q2: 0.86 (0.76, 0.97) Q3: 0.77 (0.67, 0.88) Q4: 0.75 (0.65, 0.86) Q5: 0.75 (0.65, 0.88)	

Song et al. (2004), the US	8.8 years	37309	100	Q1: 24.8 Q5: 27.1 (Values divided into 5 groups by total meat)	(53.5-54.6)	Not reported	Not reported	1558 (4.2)	Self-report, validation in subgroups via blood samples and telephone interviews according to the ADA criteria	Validated FFQ	SFA	Q1: 13.8 g/d Q2: 17.1 g/d Q3: 19.4 g/d Q4: 21.8 g/d Q5: 25.8 g/d	Q1: 1.00 (reference) Q2: 0.95 (0.76, 1.18) Q3: 0.94 (0.73, 1.21) Q4: 0.85 (0.64, 1.13) Q5: 0.89 (0.66, 1.21)	Age, BMI, total energy intake, smoking, exercise, alcohol use, family history of diabetes, fiber intake, glycemic load, magnesium and total fat
											MUFA	Q1: 15.1 g/d Q2: 18.9 g/d Q3: 21.4 g/d Q4: 24.0 g/d Q5: 27.9 g/d	Q1: 1.00 (reference) Q2: 1.01 (0.77, 1.32) Q3: 1.11 (0.80, 1.55) Q4: 1.17 (0.81, 1.70) Q5: 1.27 (0.85, 1.91)	
											Omega-3	Q1: 0.95 g/d Q2: 1.17 g/d Q3: 1.34 g/d Q4: 1.54 g/d Q5: 1.88 g/d	Q1: 1.00 (reference) Q2: 1.09 (0.92, 1.29) Q3: 1.06 (0.89, 1.25) Q4: 1.13 (0.96, 1.34) Q5: 1.10 (0.93, 1.30)	
											Omega-6	Q1: 7.35 g/d Q2: 9.12 g/d Q3: 10.5 g/d Q4: 12.0 g/d Q5: 14.5 g/d	Q1: 1.00 (reference) Q2: 1.06 (0.89, 1.26) Q3: 1.09 (0.91, 1.31) Q4: 1.04 (0.86, 1.25) Q5: 0.95 (0.78, 1.16)	
van et al. (2002), the US	12 years	42504	0	Q1: 24.6 Q5: 26.0 (Values divided into 5 groups by SFA)	(40-75)	Not reported	Not reported	1321 (3.1)	Self-report, validation according to WHO criteria (1985)	Validated FFQ	Total fat	Q1: 24% Q2: 29% Q3: 32% Q4: 35% Q5: 39%	Q1: 1.00 (reference) Q2: 0.99 (0.81, 1.21) Q3: 1.14 (0.94, 1.39) Q4: 1.00 (0.82, 1.22) Q5: 0.97 (0.79, 1.18)	Age, total energy intake, time period, physical activity, cigarette smoking, alcohol consumption, hypercholesterolemia, hypertension, family history of diabetes, cereal fiber, magnesium and BMI
											SFA	Q1: 7.6% Q2: 9.6% Q3: 11% Q4: 12% Q5: 14%	Q1: 1.00 (reference) Q2: 1.20 (0.98, 1.46) Q3: 1.12 (0.92, 1.38) Q4: 1.22 (1.00, 1.49) Q5: 0.97 (0.79, 1.20)	
											Long-chain omega.3	Q1: 80 mg/d Q2: 155 mg/d Q3: 250 mg/d Q4: 350 mg/d Q5: 570 mg/d	Q1: 1.00 (reference) Q2: 1.01 (0.85, 1.19) Q3: 0.95 (0.79, 1.13) Q4: 1.05 (0.88, 1.25) Q5: 1.01 (0.84, 1.21)	
van et al. (2009), Netherlands	12.4 years	4472	41.5	Q1: 26.1 Q2: 26.3 Q3: 26.4 Q4: 26.2 (Values divided into 4 groups by long-chain omega-3)	67.2 *(Mean of Q2 and Q3 when divided into 4 groups by fish intake)	Q1: 45.1 Q2: 44.1 Q3: 43.9 Q4: 43.3 (Values divided into 4 groups by long-chain omega-3)	Q1: 36.7 Q2: 36.9 Q3: 36.5 Q4: 35.9 (Values divided into 4 groups by long-chain omega-3)	463 (10.4)	Defined according to WHO (1999) and ADA criteria (1997)	Validated FFQ	Long-chain omega-3	T1: 23.8 mg/d T2: 89.4 mg/d T3: 236.8 mg/d	T1: 1.00 (reference) T2: 1.06 (0.84, 1.34) T3: 1.05 (0.80, 1.38)	Age, sex, smoking, education level, intake of energy, alcohol, TFA, fiber, selenium, Vitamin D and cholesterol

Villegas et al. (2011), China, women	8.9 years	64193	55.3	Q1: 24.3 Q2: 23.8 Q3: 23.7 Q4: 23.6 Q5: 23.6 (Values divided into 5 groups by Long-chain omega-3)	(40-70)	Not reported	Not reported	2262 (3.5)	Self-report and confirmation according to ADA criteria	Validated FFQ	Long-chain omega-3	Q1: 0.02 g/d Q2: 0.04 g/d Q3: 0.07 g/d Q4: 0.11 g/d Q5: 0.20 g/d	Q1: 1.00 (reference) Q2: 0.90 (0.80, 1.00) Q3: 0.84 (0.75, 0.94) Q4: 0.87 (0.77, 0.98) Q5: 0.84 (0.74, 0.95)	Age, energy intake, WHR, BMI, smoking, alcohol consumption, physical activity, income level, education level, occupation, family history of diabetes, hypertension and dietary pattern
Villegas et al. (2011), China, men	4.1 years	51963		Q1: 23.4 Q2: 23.6 Q3: 23.6 Q4: 23.7 Q5: 23.7 (Values divided into 5 groups by Long-chain omega-3)	(40-74)			833 (1.6)				Q1: 0.02 g/d Q2: 0.04 g/d Q3: 0.07 g/d Q4: 0.11 g/d Q5: 0.20 g/d	Q1: 1.00 (reference) Q2: 0.95 (0.77, 1.17) Q3: 0.86 (0.69, 1.07) Q4: 0.96 (0.77, 1.19) Q5: 0.89 (0.70, 1.12)	
Virtanen et al. (2014), Finland	19.3 years	2212	0	Q1: 26.4 Q4: 26.9 (Values divided into 4 groups by EPA + DPA + DHA)	(42-60)	Not reported	Not reported	422 (19.1)	Self-report, fasting plasma glucose ≥ 7.0mmol/L or 2-h oral glucose tolerance test plasma glucose ≥ 11.1 mmol/L, record linkage	4-day food record	Long-chain omega-3	Q1: <0.05 g/d Q2: 0.05-0.19 g/d Q3: 0.20-0.43 g/d Q4: >0.43 g/d	Q1: 1.00 (reference) Q2: 0.80 (0.61, 1.06) Q3: 0.91 (0.70, 1.19) Q4: 0.85 (0.65, 1.12)	Age, examination year, BMI, family history of diabetes, smoking, education years, leisure-time physical activity, intake of alcohol, serum linoleic acid and energy
Zheng et al. (2019), China	5.6 years	2671	68.8	23.2	(40-75)	Not reported	Not reported	213 (8.0)	Defined according to ADA criteria	Validated FFQ	Long-chain omega-3	Q1: 0.021 g/d Q2: 0.042 g/d Q3: 0.068 g/d Q4: 0.12 g/d	Q1: 1.00 (reference) Q2: 0.75 (0.50, 1.14) Q3: 0.87 (0.59, 1.29) Q4: 0.78 (0.52, 1.19)	Age, sex, BMI, WHR, physical activity, education, alcohol, smoking, household income, family history of diabetes, total energy intake, intake of dairy products, red and processed meat, fruits and vegetables, fasting blood glucose and erythrocyte total n-6 PUFA

Zong et al. (2019), the US, women (NHS)	32 years	83648	100	Q1: 24.1 Q3: 24.4 Q5: 24.3 (Values divided into 5 groups by n-6 PUFA)	(30-55)	Q1: 39.8 Q3: 38.8 Q5: 38.3 (Values divided into 5 groups by n-6 PUFA)	Q1: 34.3 Q3: 38.7 Q5: 43.2 (Values divided into 5 groups by n-6 PUFA)	9375 (11.2)	Self-report, validated according to the National Diabetes Data Group criteria	Validated FFQ	Omega-6	Q1: 2.62% Q2: 3.47% Q3: 4.16% Q4: 4.95% Q5: 6.32%	Q1: 1.00 (reference) Q2: 0.95 (0.89, 1.02) Q3: 1.00 (0.93, 1.07) Q4: 0.94 (0.87, 1.01) Q5: 0.97 (0.90, 1.06)	Age, ethnicity, smoking status, alcohol intake, family history of diabetes, menopausal status and postmenopausal hormone use, physical activity, multivitamin use, baseline hypertension, baseline hypercholesterolemia, updated BMI, total energy intake, intake of fruits and vegetable, total fat, trans fats, monounsaturated fats, other PUFAs
Zong et al. (2019), the US, women (NHS2)	32 years	88610	100	Q1: 24.0 Q3: 24.5 Q5: 24.9 (Values divided into 5 groups by n-6 PUFA)	(25-44)	Q1: 54.1 Q3: 49.6 Q5: 46.2 (Values divided into 5 groups by n-6 PUFA)	Q1: 25.4 Q3: 30.4 Q5: 35.2 (Values divided into 5 groups by n-6 PUFA)	5460 (6.2)				Q1: 3.41% Q2: 4.17% Q3: 4.76% Q4: 5.43% Q5: 6.60%	Q1: 1.00 (reference) Q2: 0.93 (0.85, 1.02) Q3: 0.91 (0.82, 1.00) Q4: 0.94 (0.85, 1.04) Q5: 0.91 (0.80, 1.02)	
Zong et al. (2019), the US, men (HPFS)	26 years	41771	0	Q1: 24.8 Q3: 25.0 Q5: 24.9 (Values divided into 5 groups by n-6 PUFA)	(40.75)	Q1: 50.3 Q3: 46.6 Q5: 43.9 (Values divided into 5 groups by n-6 PUFA)	Q1: 25.3 Q3: 30.6 Q5: 35.6 (Values divided into 5 groups by n-6 PUFA)	3607 (8.6)				Q1: 3.53% Q2: 4.43% Q3: 5.13% Q4: 5.91% Q5: 7.24%	Q1: 1.00 (reference) Q2: 0.86 (0.77, 0.96) Q3: 0.90 (0.80, 1.01) Q4: 0.82 (0.73, 0.92) Q5: 0.74 (0.65, 0.85)	

Nanri et al. (2015), Japan, men	5 years	27799	57.0	Q1: 23.3 Q3: 23.6 Q5: 23.8 (Values divided into 5 groups by low carbohydrate diet score)	(40-59)	Q1: 64.7 Q3: 51.6 Q5: 43.7 (Values divided into 5 groups by low carbohydrate diet score)	Q1: 15.8 Q3: 22.7 Q5: 32.5 (Values divided into 5 groups by low carbohydrate diet score)	691 (2.5)	Self-reported	Validated FFQ	Total fat	Q1: 14.4% Q2: 19.2% Q3: 22.8% Q4: 26.4% Q5: 32.4%	Q1: 1.00 (reference) Q2: 1.13 (0.87, 1.46) Q3: 1.03 (0.76, 1.39) Q4: 1.11 (0.79, 1.56) Q5: 0.90 (0.57, 1.43)	Age, study area, smoking status (never, past, current with a consumption of<20 or ≧ 20 cigarettes/day), alcohol consumption (nondrinker,occasional drinker, or drinker with a consumption of<150, 150–299, 300–449, or ≧450 g ethanol/week), family history of diabetes mellitus (yes or no),total physical activity (quartile, metabolic equivalent-hour/day), history of hypertension (yes or no), total energy intake (kcal/day), and coffee consumption(almost never,<1, 1, or ≧ 2 cups/day), BMI (<21, 21–22.9, 23–24.9, 25–26.9, or >≧27 kg/m^2), carbohydrate
Nanri et al. (2015), Japan, women		36875		Q1: 23.5 Q3: 23.4 Q5: 23.5 (Values divided into 5 groups by low carbohydrate diet score)	(40-59)	Q1: 67.2 Q3: 55.7 Q5: 44.9 (Values divided into 5 groups by low carbohydrate diet score)	Q1: 18.7 Q3: 27.7 Q5: 35.9 (Values divided into 5 groups by low carbohydrate diet score)	500 (1.4)				Q1: 18.9% Q2: 23.9% Q3: 27.2% Q4: 30.7% Q5: 36.1%	Q1: 1.00 (reference) Q2: 1.00 (0.73, 1.37) Q3: 0.90 (0.61, 1.33) Q4: 1.06 (0.67, 1.69) Q5: 0.91 (0.48, 1.72)	

*1 If the subjects' full values were not reported in the paper, the values were grouped by exposure factor nutrients and other factors.

Table 5. Characteristics of the studies included in the systematic review and meta-analysis for association low carbohydrate diet score with the incidence risk of type 2 diabetes

Author, (publish year), country	Follow-up	Sample size, n	Women (%)	Mean BMI*[1]	Mean age (age range)	Carbohydrate (% energy)*[1]	Fat (%energy)*[1]	Incident diabetes, n (%)	Diabetes Assessment method	Dietary Assessment	Exposure *[3]	OR/RR/HR (95% CI)	Adjustment factors
Bao et al. (2016), the US	12 years	4502	100	Q1: 25.4 Q2: 26.2 Q3: 26.6 Q4: 27.4 Q5: 29.1	(24-44)	Q1: 57.3 Q2: 52.3 Q3: 49.6 Q4: 46.0 Q5: 42.0	Q1: 27.3 Q2: 29.8 Q3: 31.9 Q4: 34.4 Q5: 36.9	722 (16.0)	American Diabetes Association criteria: a) one or more classic symptoms plus FBS>7.0 mmmol/l or random plasma glucose >11.1mmol/l), 2) no symptoms reported but 2 or more than one occation or 3) treatment with insulin or oral hypoglycemic agent	Validated repeated FFQ	Overall low carbohydrate diet score	Q1: 1.00 (reference) Q2: 0.95 (0.70, 1.30) Q3: 1.02 (0.77, 1.36) Q4: 1.28 (0.96, 1.71) Q5: 1.36 (1.04, 1.78)	Age (months), parity (1, 2, 3,≧4), age at first birth (12–24, 25–29, ≧ 30 years), race/ethnicity (Caucasian, African American, Hispanic, Asian, other), family history of diabetes (yes or no), oral contraceptive use (current, former, never), menopausal status (premenopausal or postmenopausal), cigarette smoking (never, former, current), alcohol intake (0, 0.1–4.9, 5.0–14.9, ≧ 15.0 g/day), physical activity (quintiles), total energy intake (quintiles), glycemic index, and BMI(,23.0, 23.0–24.9, 25.0–26.9, 27.0–29.9, 30.0–34.9, 35.0–39.9, or ≧40.0 kg/m^2)
											Animal low carbohydrate diet score	Q1: 1.00 (reference) Q2: 0.97 (0.71, 1.32) Q3: 1.12 (0.84, 1.50) Q4: 1.18 (0.88, 1.58) Q5: 1.40 (1.06, 1.84)	
											Vegetable low carbohydrate diet score	Q1: 1.00 (reference) Q2: 1.38 (1.05, 1.81) Q3: 1.24 (0.94, 1.63) Q4: 1.14 (0.86, 1.51) Q5: 1.19 (0.91, 1.55)	
de et al. (2011), the US	20 years	40475	0	Q1: 24.7 Q5: 26.2	(40–75)	Q1: 57.7 Q5: 37.3	Q1: 25.6 Q5: 38.6	2689 (6.6)	*4 Before 1998 were used from the National Diabetes Data Group criteria, *5 After 1998 used were American Diabetes Association criteria	Validated repeated FFQ	Overall low carbohydrate diet score	Q1: 1.00 (reference) Q2: 1.03 (0.89, 1.19) Q3: 1.14 (0.99, 1.31) Q4: 1.17 (1.02, 1.33) Q5: 1.31 (1.14, 1.49)	Age, smoking [never, past, current (1–15 or .15 cigarettes/d), or missing], physical activity (quintiles of metabolic equivalents/wk or missing), coffee intake (quintiles), alcohol intake (abstainers or 0–10, 10–20, or .20 g/d), family history of T2D, total energy intake (quintiles of kcal/d), and BMI (in kg/m^2 ; ,23, 23–23.9, 24–24.9, 25–26.9, 27–28.9, 29–30.9, 31–32.9, 33–34.9, ≧35, or missing
											Animal low carbohydrate diet score	Q1: 1.00 (reference) Q2: 1.13 (0.97, 1.30) Q3: 1.22 (1.08, 1.40) Q4: 1.26 (1.09, 1.44) Q5: 1.37 (1.20, 1.58)	
											Vegetable low carbohydrate diet score	Q1: 1.00 (reference) Q2: 0.90 (0.79, 1.02) Q3: 0.96 (0.85, 1.08) Q4: 0.94 (0.83, 1.06) Q5: 0.95 (0.84, 1.07)	

Halton et al. (2008), the US	20 years	85059	100	D1: 24.0 D5: 24.0 D10: 24.7	(30-55)	D1: 54.7 D5: 43.4 D10: 29.6	D1: 28.3 D5: 35.2 D10: 46.1	4670 (5.5)	American Diabetes Association criteria *2	Validated repeated FFQ	Overall low carbohydrate diet score	Q1: 1.00 (reference) Q2: 0.98 (0.85, 1.12) Q3: 0.96 (0.84, 1.10) Q4: 0.92 (0.81, 1.05) Q5: 0.90 (0.78, 1.04)	Age in 5-y categories, smoking (never, past, or current smoking of 1–14, 15–24, or ≧ 25 cigarettes/d), postmenopausal hormone use (never, current use, past use), physical activity (<1, 1–2, 2–4, 4–7, or >7 h/wk), alcohol intake (0, 1–4.9, 5–14.9, or ≧15 g/d), and family history of type 2 diabetes in a first-degree relative, and BMI (<22, 22–22.9, 23–23.9, 24–24.9, 25–27.9, 28–29.9, 30–31.9, 32–33.9, 34–39.9, or ≧40 kg/m^2)
											Animal low carbohydrate diet score	Q1: 1.00 (reference) Q2: 1.05 (0.92, 1.21) Q3: 1.02 (0.89, 1.17) Q4: 1.03 (0.90, 1.18) Q5: 0.99 (0.85, 1.16)	
											Vegetable low carbohydrate diet score	Q1: 1.00 (reference) Q2: 0.82 (0.72, 0.94) Q3: 0.85 (0.74, 0.97) Q4: 0.83 (0.73, 0.94) Q5: 0.82 (0.71, 0.94)	
Sali et al. (2020), Iran	3 years	4356	55.6	27.1	40.5 ± 13.0	Q1: 64.7 Q2: 58.2 Q3: 52.1 Q4: 46.8	Q1: 23.6 Q2: 27.9 Q3: 32.7 Q4: 35.7	123 (2.8)	FPG ≥ 126 mg/dl or 2-h post 75 g glucose load ≥ 200 mg/dl or being on oral hypoglycemic medication	Validated FFQ	Overall low carbohydrate diet score	Q1: 1.00 (reference) Q2: 1.50 (0.89, 2.52) Q3: 1.26 (0.67, 2.34) Q4: 2.16 (1.16, 4.04)	Age and sex, waist circumference, physical activity, educational level, smoking (yes or no), daily energy intake, and family history of diabetes
											Animal low carbohydrate diet score	Q1: 1.00 (reference) Q2: 1.59 (0.93, 2.72) Q3: 1.25 (0.70, 2.24) Q4: 1.81 (1.06, 3.11)	
											Vegetable low carbohydrate diet score	Q1: 1.00 (reference) Q2: 1.14 (0.66, 1.95) Q3: 1.30 (0.75, 2.22) Q4: 1.47 (0.85, 2.52)	

Nanri et al. (2015), Japan, men	5 years	27799	0	Q1: 23.3 Q3: 23.6 Q5: 23.8	(40-59)	Q1: 64.7 Q3: 51.6 Q5: 43.7	Q1: 15.8 Q3: 22.7 Q5: 32.5	691 (2.5)	Self-reported	Validated FFQ	Overall low carbohydrate diet score	Q1: 1.00 (reference) Q2: 1.09 (0.85, 1.40) Q3: 1.16 (0.92, 1.48) Q4: 1.10 (0.86, 1.42) Q5: 1.00 (0.77, 1.30)	Age, study area, smoking status (never, past, current with a consumption of<20 or ≧ 20 cigarettes/day), alcohol consumption (nondrinker,occasional drinker, or drinker with a consumption of<150, 150–299, 300–449, or ≧ 450 g ethanol/week), family history of diabetes mellitus (yes or no),total physical activity (quartile, metabolic equivalent-hour/day), history of hypertension (yes or no), total energy intake (kcal/day), and coffee consumption(almost never,<1, 1, or≧2 cups/day), BMI (<21, 21–22.9, 23–24.9, 25–26.9, or ≧27 kg/m²)
											Animal low carbohydrate diet score	Q1: 1.00 (reference) Q2: 1.10 (0.86, 1.41) Q3: 1.21 (0.95, 1.54) Q4: 1.06 (0.83, 1.36) Q5: 1.03 (0.80, 1.34)	
											Vegetable low carbohydrate diet score	Q1: 1.00 (reference) Q2: 0.91 (0.72, 1.17) Q3: 0.99 (0.79, 1.24) Q4: 0.88 (0.69, 1.13) Q5: 0.79 (0.62, 1.01)	
Nanri et al. (2015), Japan, women		36875	100	Q1: 23.5 Q3: 23.4 Q5: 23.5	(40-59)	Q1: 67.2 Q3: 55.7 Q5: 44.9	Q1: 18.7 Q3: 27.7 Q5: 35.9	500 (1.4)			Overall low carbohydrate diet score	Q1: 1.00 (reference) Q2: 0.93 (0.72, 1.20) Q3: 0.71 (0.54, 0.94) Q4: 0.71 (0.53, 0.97) Q5: 0.63 (0.46, 0.84)	
											Animal low carbohydrate diet score	Q1: 1.00 (reference) Q2: 0.89 (0.69, 1.16) Q3: 0.97 (0.74, 1.27) Q4: 0.70 (0.52, 0.94) Q5: 0.64 (0.48, 0.87)	
											Vegetable low carbohydrate diet score	Q1: 1.00 (reference) Q2: 1.05 (0.79, 1.38) Q3: 0.98 (0.74, 1.30) Q4: 0.91 (0.68, 1.21) Q5: 0.81 (0.61, 1.08)	

*1 If the subjects' full values were not reported in the paper, the values were determined based on normal low carbohydrate diet score

*2 : A diagnosis of type 2 diabetes was defined by at least one of the following criteria reported on the supplemental questionnaire:1) ≧1 classic symptom (excessive thirst, polyuria, hunger, or weight loss) plus a fasting plasma glucose concentration of ≧140 mg/dL (7.8 mmol/L) or a random plasma glucose concentration of ≧200 mg/dL (11.1 mmol/L); 2) ≧2 elevated plasma glucose concentrations on different occasions [fasting≧140 mg/dL (7.8 mmol/L), random ≧ 200 mg/dL (11.1 mmol/L)] or random ≧200 mg/dL (11.1 mmol/L) after≧2 h of oral-glucose-tolerance testing in the absence of symptoms; or 3) treatment with hypoglycemic medications (insulin or oral hypoglycemic agents)

*3 Normal low carbohydrate diet score: Sum of carbohydrate, total fat, and total protein scores

Animal low carbohydrate diet score: Sum of carbohydrate, animal fat, and animal protein scores

Vegeteble low carbohydrate diet score: Sum of carbohydrate, vegetable fat, and vegetable protein scores

*4 1. Symptoms of diabetes plus casual plasma glucose concentration >200 mg/dl (11.1 mmol/1). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

or

2. FPG≧126 mg/dl (7.0 mmol/1). Fasting is defined as no caloric intake for at least 8 h.

or

3. 2hPG≧200 mg/dl during an OGTT. The test should be performed as described by WHO (2), using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.

*5 A case of diabetes was considered confirmed if at least 1 of the following was reported on the supplementary questionnaire: (1) 1 or more classic symptoms (excessive thirst, polyuria, weight loss, hunger) plus 1 fasting plasma glucose level of at least 7.8 mmol/L (140 mg/dL) or random plasma glucose of at least 11.1 mmol/L (200 mg/dL); (2) at least 2 elevated plasma glucose concentrations on different occasions (fasting, ≧7.8 mmol/L [≧140 mg/dL]; random, ≧11.1 mmol/L [>=200 mg/dL]; and/or ≧11.1 mmol/L [≧200 mg/dL] after ≧2 hours of oral glucose tolerance testing) in the absence of symptoms; or (3) treatment with hypoglycemic medication (insulin or oral hypoglycemic agent).

1.4. Discussion

This review study provided an overview of the association of carbohydrate and fat intakes as exposure factors with the incidence risk of type 2 diabetes to date, and the following four main points became clear.

The first point found was a shortage of studies in Asia regarding the association of total fat, SFA, MUFA, PUFA, n-6 PUFA, n-3 PUFA, and "low carbohydrate diet score" with incidence risk of type 2 diabetes. A review of carbohydrate reported 13 studies in all countries, of these, six were from Asia. On the other hand, a review of fat reported 8 studies (Asia 2) for total fat, 11 studies (Asia 1) for SFA, 10 studies (Asia 1) for MUFA, 8 studies (Asia 0) for PUFA, 6 studies (Asia 1) for n-6 PUFA, 12 studies (Asia 3) for n-3 PUFA. Also, a review of low carbohydrate diet score reported 5 studies (Asia 2).

The second point found the association of carbohydrate intake with type 2 diabetes differed between Asians and non-Asians. (Asian: RR = 1.29, 95% CI 1.15, 1.45, non-Asian: RR = 0.92, 95% CI 0.83, 1.01) (Yaegashi and Sunohara et al, 2023). These discrepancies may be due to differences in the amount of carbohydrate intake between Asians and non-Asians. Asians have a higher carbohydrate intake compared to non-Asians (Dehghan et al, 2017; Zhou et al, 2003). In addition, Asians have lower insulin secretory capacity compared to non-Asians (Kadowaki et al, 1984).

The third point found, for association with fat and low carbohydrate diet score and type 2 diabetes, the previous meta-analysis did not conduct sub-analysis (Hosseini et al, 2023; Neuenschwander et al, 2020). This may be due to the lack of research on Asia. Because compared to non-Asians, Asians have a higher carbohydrate and lower fat intake (Dehghan et al, 2017; Zhou et al, 2003), and lower insulin secretory capacity (Kadowaki et al, 1984), association with fat and low carbohydrate diet score and diabetes may differ between Asians and non-Asians as well as carbohydrates (Yaegashi and Sunohara et al, 2023).

The fourth point found, for the common characteristics of the three exposure factors (carbohydrate, fat, and low carbohydrate diet score), several non-Asian studies reported long follow-up periods, larger numbers of participants, and repeated FFQ (Kaushik et al, 2009; Kaushik et al, 2009; Halton et al. Van et al, 2002, Bao et al, 2016, de et al, 2011; Salmerón et al, 2001; AlEssa et al, 2015). On the other hand, no such study had been conducted in Asia.

In conclusion, among Asians such as Japanese, 1) for association with fat and low carbohydrate diet score and type 2 diabetes, further research is needed; 2) for association with carbohydrate, fat, and low carbohydrate diet score and type 2 diabetes, long follow-up periods, larger numbers of participants, and repeated FFQ studies is needed.

Chapter 2: Association between total fat and fatty acids and incidence of type 2 diabetes among Japanese adults: the JACC study

2.1. Introduction

Review study in chapter 1 revealed that, among Asians such as Japanese, further research is needed to investigate the relationship between total fat and fatty acids intakes and type 2 diabetes.

As shown in overall introduction, different types of fatty acids may affect diabetes risk. For example, in experimental evidence suggests that n-6 PUFA and n-3 PUFA were associated with favorable protection against the development of type 2 diabetes (Maki et al, 2018; Borkman et al, 1993), but SFA induces insulin resistance (Boden, 1997). However, as shown in chapter 1, a previous meta-analysis reported that total fat and all fatty acids were not associated with the incidence of diabetes.

Most of the studies included in this meta-analysis were conducted in non-Asians. Previous two studies reported that Asians have a lower fat intake compared to non-Asians (Table 6) (Dehghan et al, 2017; Zhou et al, 2003). In addition, food sources of nutrients were different between Asians and non-Asians (Anderson et al, 2010). Thus, the results of the previous meta-analysis study may not apply to Asia such as Japan.

Table 6. Comparison of energy from total fat between Asia and non-Asia

Reference	Asia	Non-Asia
Zhou et al, 2003	Japan (men): 23.7% energy	United Kingdom (men): 33.0% energy
	China (men): 20.5% energy	The US (men): 33.3% energy
	Japan (women): 26.1% energy	United Kingdom (women): 32.5% energy
	China (women): 19.5% energy	The US (women): 32.6% energy
Dehghan et al, 2017	China: 17.7% energy	Europe and North America: 30.5% energy
	South Asia: 20.5% energy	

Therefore, in this chapter, the aim was to clarify the association between total fat and fatty acids intakes and the type 2 diabetes risk in Japanese adults in Asia using JACC Study data.

2.2. Methods

2.2.1. Study design and population

This research was conducted using JACC study data (Tamakoshi et al, 2005; Tamakoshi et al, 2013). The study was conducted from 1988 through 1990 with participants aged 40–

79 years and was a multicenter collaborative study in which 24 institutions voluntarily participated to evaluate the risk impact of lifestyle factors and levels of serum components on human health.

The study was established in 45 areas across Japan, spread out as follows: three towns in the Hokkaido district, five towns in the Tohoku district, five towns in the Kanto district, one city, three towns, and two villages in the Chubu district, eight towns and two villages in the Kinki district, one city and one town in the Chugoku district, and four cities, nine towns, and one village in the Kyushu district.

An interim survey on lifestyle factors was conducted in 31 areas, about five years after the baseline survey. The survey was performed using a self-administered questionnaire that covered demographic information, past medical history, family cancer history in the past five years, exercise/sports activities, frequency of food intake and changes in intake compared to five years prior, hair dye use, smoking and alcohol drinking status, and health checkup history. It's worth noting that no blood samples were collected this time.

Although the study's follow-up ended in 2009, the results were analyzed and published in nearly 200 peer-reviewed articles in English-language journals.

2.2.2. Ethical issues

In 36 of the 45 study areas covered in the JACC, informed consent was obtained from each participant before enrollment into the study. Consent was obtained from the leader of each remaining area as a group. The study protocol followed the guidelines of the Declaration of Helsinki and received approval from the Ethics Committee of Hokkaido University's Faculty of Medicine, with the assigned approval number being 14-044.

2.2.3. Assessment of dietary intake

The participants were asked to report their consumption of 40 food and drink items over the past year in FFQ (Date et al, 2005). The FFQ had five possible response options ranging from rarely to almost every day (rarely, 1–2 times/month, 1–2 times/week, 3–4 times/week, and almost every day). The validation study to evaluate of dietary intake over a one-year period using four three-day weighted dietary records of 85 participants (eight men and 77 women) was used as a reference to estimate size of each meal portion and obtain data on the validity of the FFQ-estimated intakes. Previously reported, the FFQ-estimated energy-adjusted total fat and fatty acids intakes showed moderate correlation with the ones estimated from dietary records in the validation study (Date et al, 2005). The Spearman rank correlation coefficients were: 0.46 for total fat, 0.50 for SFA, 0.36 for MUFA, 0.15 for PUFA, 0.21 for n-3 PUFA, and 0.16 for n-6 PUFA. Intake of energy and nutrients such as total fat and fatty acids were computed using the Standard Tables of

Food Composition in Japan, 5th Revised and Enlarged Edition (The Council for Science and Technology, Ministry of Education Culture, Sports, Science and Technology, Japan, 2005).

2.2.4. Assessment of diabetic status

The five-year cumulative incidence of diabetes was used for analysis because the exact dates of the diabetes diagnoses of the participants were unknown. Therefore, an individual with incident diabetes was a participant who did not have diabetes at baseline but reported physician-diagnosed diabetes by the fifth follow-up year. In a sample 1230 men and 1837 women, the diagnosis of diabetes that was self-reported has been confirmed by comparing it with therapy data and laboratory findings. The sensitivity and specificity were found to be 70% and 95% for men and 75% and 98% for women, respectively (Iso et al, 2006).

2.2.5. Assessment of other factors

The baseline self-administered questionnaire consisted of questions regarding lifestyle factors, such as current smoking and drinking habits, hours spent exercising and walking, medical history of diabetes, cancer, or myocardial infarction, family history of diabetes and hypertension, height, and weight. To determine the BMI, self-reported weight in kilograms was divided by the square of self-reported body height in meters.

2.2.6. Statistical analysis

Six nutrients intake were examined (Total fat, SFA, MUFA, PUFA, n-3 PUFA, and n-6 PUFA). Men and women were analyzed separately because the Japanese dietary intake differs according to sex (men: 2118 kcal; total fat 66.4 g; women: 1709 kcal; total fat 56.7 g) (Ministry of Health, Labor and Welfare of Japan).

To analyze the relationship between the intake of total fat and fatty acids and various factors, we categorized the intake into five groups. We used the Mantel-Haenszel chi-squared test for categorical variables and linear regression analysis for continuous variables, with the median intake in each quintile category of total fat and fatty acids intakes. Multivariable logistic regression was performed to evaluate the association between fat intake and the risk of type 2 diabetes. The lowest quintile of fat intake was used as the reference group for the analysis. Model 1 was adjusted for age and stratified jointly according to area of residence (Hokkaido, Tohoku, Kanto, Chubu, Kinki, Chugoku, and Kyushu). Model 2 was additionally adjusted for family history of diabetes (yes, no), family history of hypertension (yes, no), smoking status (never, former smoker, current smoker), BMI (<18.5, 18.5–24.9, 25.0–30.0, >30.0 kg/m^2), hours of walking (almost none, daily 0.5, 0.6–0.9, and ≥1.0 h), hours of exercise (almost none, weekly 1–2, 3–4, and ≥5 h), alcohol consumption (never, former drinker, current drinker), energy intake (kcal, continuous), and carbohydrate (g/day, continuous). An indicator variable for missing data was created for each covariate. To calculate the P value for linear trend, we used a continuous variable of total fat and fatty acids intakes assigning the median values in each quartile. P (two-tailed) <0.05 was considered statistically significant. Statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc.).

2.3. Results

The JACC study had 110,585 participants who completed the questionnaire. The present study excluded those who were from areas not investigated on total fat and fatty acids intakes (n = 24,184), those with missing dietary data (n = 24,614), those who reported extreme energy intakes (<500 kcal or >3500 kcal) (n = 159), those with a medical history of diabetes, cancer, or myocardial infarction at baseline (n = 9,335), those living in areas not investigated for the development of diabetes after five years of follow-up (n = 5,044), and those who did not provide data on diabetes at the fifth year follow-up survey (n = 28,161). Thus, a total of 19,088 participants (7,044 men and 12,044 women) were included in the present study.

2.3.1. The baseline characteristics of the participants

During the study period, a total of 494 (2.6%) participants (men, n = 247 [3.5%]; women, n = 247 [2.0%]) developed type 2 diabetes. The baseline characteristics of the study population stratified according to quintiles of energy-adjusted total fat and fatty acids intakes in men and women are presented in Tables 7 (men) and 8 (women). For men, participants with higher total fat and fatty acids intakes were older, exercised for longer, and had a lower proportion of current drinkers than those with lower total fat and fatty acids intakes. For men and women, participants with higher total fat and fatty acids intakes had higher total protein intake, lower carbohydrate intake, and lower proportion of current smokers than those with lower total fat and fatty acids intakes.

Table 7. Baseline characteristics of participants according to quintiles of energy-adjusted[a] total fat and fatty acids intakes (men)

	Total fat			SFA			MUFA		
	Q1 (low)	Q3	Q5 (high)	Q1 (low)	Q3	Q5 (high)	Q1 (low)	Q3	Q5 (high)
Age, years	54.8 (9.2)	55.7 (9.4)	56.9 (9.5)**	55.1 (9.3)	55.8 (9.5)	56.5 (9.7)**	54.9 (9.3)	55.6 (9.5)	56.8 (9.4)**
Family history of diabetes, %	7.9	12.5	10.4**	8.4	11.3	11.1	8.3	12.6	10.2**
Family history of hypertension, %	35.1	36.6	34.1	35.4	36.4	34.4	35.7	37.0	34.0
Current smoker, %	57.4	50.3	47.8**	56.5	47.3	51.6**	57.1	52.2	48.8**
Current drinker, %	85.4	82.9	70.3**	84.9	76.2	70.0**	84.7	76.9	72.0**
BMI, kg/m^2	22.7 (2.6)	22.8 (4.4)	22.6 (2.6)	22.7 (2.6)	22.8 (4.4)	22.5 (2.6)	22.7 (2.6)	22.6 (2.7)	22.5 (2.7)
BMI ≥25 kg/m^2, %	18.2	18.6	16.3	17.1	18.6	15.8	17.5	16.6	16.7
Exercise ≥ 5 h/week, %	6.2	7.3	9.7	7.0	7.1	8.9	6.3	6.7	9.9**
Walking ≥ 0.5 h/week, %	86.7	86.4	89.0	86.1	87.6	89.5	86.7	87.0	89.4*
Energy intake, kcal	1920 (516)	1737 (491)	1899 (516)	1883 (526)	1757 (500)	1855 (497)	1929 (516)	1739 (500)	1906 (522)
Carbohydrate, % energy	61.3 (11.5)	57.7 (9.5)	53.4 (8.0)**	60.5 (11.6)	57.9 (9.6)	54.2 (8.4)**	61.4 (11.4)	57.5 (9.5)	53.3 (8.2)**
Total protein, % energy	9.6 (1.3)	12.7 (1.5)	15.0 (2.0)**	10.0 (1.6)	12.7 (1.9)	14.4 (2.3)**	9.8 (1.4)	12.6 (1.7)	14.9 (2.1)**
Total fat, % energy	10.4 (1.8)	16.7 (1.9)	22.9 (3.6)**	10.8 (2.2)	16.7 (2.6)	22.5 (3.9)**	10.6 (1.9)	16.7 (2.1)	22.8 (3.7)**
SFA, % energy	3.0 (0.7)	5.1 (1.0)	7.2 (1.6)**	2.9 (0.5)	5.0 (0.7)	7.6 (1.5)**	3.0 (0.7)	5.1 (1.1)	7.2 (1.6)**
MUFA, % energy	3.2 (0.6)	5.3 (0.8)	7.5 (1.4)**	3.3 (0.8)	5.3 (1.0)	7.3 (1.4)**	3.2 (0.6)	5.3 (0.7)	7.5 (1.3)**
PUFA, % energy	2.8 (0.7)	4.1 (0.8)	5.2 (1.0)**	3.1 (0.8)	4.1 (1.0)	4.7 (1.2)**	2.9 (0.8)	4.0 (0.9)	5.1 (1.0)**
n-3 PUFA, % energy	0.5 (0.2)	0.8 (0.2)	1.0 (0.3)**	0.6 (0.2)	0.8 (0.3)	0.9 (0.3)**	0.5 (0.2)	0.8 (0.2)	1.0 (0.3)**
n-6 PUFA, % energy	2.3 (0.6)	3.2 (0.7)	4.1 (0.8)**	2.5 (0.7)	3.3 (0.8)	3.8 (0.9)**	2.4 (0.7)	3.2 (0.7)	4.1 (0.8)**
	PUFA			**n-3 PUFA**			**n-6 PUFA**		
	Q1 (low)	**Q3**	**Q5 (high)**	**Q1 (low)**	**Q3**	**Q5 (high)**	**Q1 (low)**	**Q3**	**Q5 (high)**
Age, years	54.7 (9.2)	55.9 (9.4)	57.2 (9.4)**	54.3 (9.4)	55.9 (10.0)	57.3 (9.1)**	55.0 (9.2)	55.8 (9.6)	57.4 (9.5)**
Family history of diabetes, %	8.5	12.3	9.2**	8.8	10.1	9.9	8.4	11.4	8.9
Family history of hypertension, %	34.5	36.1	33.1	35.7	35.9	33.5	34.0	36.7	33.4
Current smoker, %	57.0	51.1	43.9**	56.2	51.5	47.3**	57.3	51.1	43.9**
Current drinker, %	84.3	79.6	70.8**	81.3	77.6	76.1**	84.7	77.9	69.7**
BMI, kg/m^2	22.6 (2.6)	22.7 (4.3)	22.7 (2.7)	22.6 (2.6)	22.6 (2.6)	22.8 (4.4)	22.6 (2.6)	22.7 (4.4)	22.6 (2.7)
BMI ≥25 kg/m^2, %	17.9	16	18.3	18	16.3	18.5	17.4	16.6	17.8
Exercise ≥ 5 h/week, %	7.2	7.0	10.3**	6.4	6.8	9.5**	7.3	7.3	10.4**
Walking ≥ 0.5 h/week, %	86.6	87.6	88.4**	87.1	85.9	87.9**	86.4	87.1	88.4**
Energy intake, kcal	1922 (491)	1739 (494)	1904 (552)	1905 (477)	1738 (508)	1890 (520)	1925 (490)	1735 (495)	1895 (547)
Carbohydrate, % energy	60.6 (11.5)	57.3 (9.6)	54.8 (8.3)**	61.8 (10.9)	57.5 (9.1)	53.4 (8.6)**	60.0 (11.6)	57.6 (9.7)	55.3 (8.3)**
Total protein, % energy	9.8 (1.5)	12.6 (1.5)	15.1 (2.0)**	9.7 (1.4)	12.6 (1.4)	15.2 (2.0)**	10.0 (1.7)	12.6 (1.7)	14.9 (2.1)**
Total fat, % energy	11.8 (3.3)	16.8 (3.5)	21.5 (4.2)**	12.4 (3.8)	17.0 (4.0)	20.6 (4.4)**	12.0 (3.4)	16.7 (3.5)	21.5 (4.3)**
SFA, % energy	3.9 (1.6)	5.2 (1.7)	6.2 (1.7)**	4.1 (1.8)	5.2 (1.8)	5.9 (1.7)**	3.9 (1.6)	5.1 (1.7)	6.2 (1.7)**
MUFA, % energy	3.7 (1.2)	5.3 (1.3)	6.9 (1.6)**	3.9 (1.3)	5.4 (1.5)	6.6 (1.6)**	3.8 (1.2)	5.3 (1.3)	6.9 (1.6)**
PUFA, % energy	2.5 (0.4)	4.0 (0.3)	5.6 (0.8)**	2.8 (0.6)	4.1 (0.7)	5.2 (1.0)**	2.6 (0.5)	4.0 (0.3)	5.6 (0.8)**
n-3 PUFA, % energy	0.5 (0.2)	0.8 (0.2)	1.1 (0.2)**	0.4 (0.1)	0.8 (0.1)	1.2 (0.2)**	0.5 (0.2)	0.8 (0.2)	1.0 (0.2)**
n-6 PUFA, % energy	2.0 (0.4)	3.2 (0.3)	4.5 (0.7)**	2.3 (0.6)	3.3 (0.7)	4.0 (0.9)**	2.0 (0.4)	3.2 (0.2)	4.5 (0.6)**

All values are mean (SD) or percentages.

aTotal fat and fatty acid levels were adjusted for energy intake using the nutrient residual model.

P-trend was calculated using the Mantel-Haenszel chi-squared test for categorical variables and linear regression analysis for continuous variables, with the median intake in each quintile category of total fat and fatty acids intakes.

*<0.05, **<0.01

Participants with missing information were excluded (BMI: n = 206; smoking status: n = 117; drinking status: n = 0; sports information: n = 134; walking information: n = 181).

Table 8. Baseline characteristics of participants according to quintiles of energy-adjusted[a] total fat and fatty acids intakes (women)

	Total fat			SFA			MUFA		
	Q1 (low)	Q3	Q5 (high)	Q1 (low)	Q3	Q5 (high)	Q1 (low)	Q3	Q5 (high)
Age, years	57.0 (9.6)	55.1 (9.3)	54.6 (9.2)**	57.5 (9.4)	55.6 (9.3)	54.3 (9.3)**	57.3 (9.5)	55.2 (9.3)	54.4 (9.2)**
Family history of diabetes, %	9.7	11.0	11.0	9.5	11.0	12.1*	10.3	10.8	11.0
Family history of hypertension, %	33.1	36.3	36.6**	32.8	37.2	37.2**	33.1	37.7	36.4**
Current smoker, %	5.6	3.0	2.8**	4.8	2.7	3.5**	5.1	2.9	2.8**
Current drinker, %	25.2	24.5	25.7	23.2	23.6	28.9**	24.5	23.5	26.4
BMI, kg/m^2	23.0 (6.4)	22.9 (2.9)	22.6 (2.8)	23.1 (6.4)	22.9 (2.9)	22.5 (2.7)**	22.9 (3.1)	22.9 (6.2)	22.6 (2.8)**
BMI ≥25 kg/m^2, %	22.6	20.9	18.1	23.5	21.1	16.0	21.7	20.5	17.7
Exercise ≥ 5 h/week, %	4.6	3.3	5.5**	5.2	3.8	4.8	4.9	3.7	5.1*
Walking ≥ 0.5 h/week, %	87.4	86.1	87.8**	87.5	87.4	89.2**	87.7	86.6	88.0**
Energy intake, kcal	1544 (422)	1378 (323)	1546 (368)	1526 (412)	1401 (341)	1520 (357)	1544 (414)	1383 (332)	1542 (371)
Carbohydrate, % energy	71.2 (6.1)	62.5 (3.7)	54.8 (4.4)**	70.4 (6.2)	62.5 (4.5)	56.0 (5.0)**	71.1 (6.0)	62.5 (3.9)	55.0 (4.5)**
Total protein, % energy	11.9 (1.5)	15.0 (1.5)	17.0 (1.9)**	12.5 (1.9)	15.0 (1.9)	16.3 (2.1)**	12.1 (1.7)	15.0 (1.7)	16.8 (2.0)**
Total fat, % energy	13.7 (2.4)	20.7 (1.1)	27.0 (2.8)**	14.2 (2.9)	20.7 (2.4)	26.3 (3.2)**	13.9 (2.6)	20.7 (1.5)	26.8 (2.9)**
SFA, % energy	4.0 (0.9)	6.4 (0.9)	8.6 (1.4)**	3.8 (0.7)	6.4 (0.4)	8.9 (1.2)**	4.1 (1.0)	6.4 (1.0)	8.5 (1.5)**
MUFA, % energy	4.2 (0.9)	6.6 (0.6)	8.9 (1.1)**	4.4 (1.0)	6.6 (1.0)	8.6 (1.3)**	4.2 (0.8)	6.6 (0.4)	9.0 (1.1)**
PUFA, % energy	3.5 (0.8)	4.8 (0.8)	5.8 (1.0)**	3.9 (1.1)	4.8 (1.1)	5.2 (1.1)**	3.6 (0.9)	4.8 (0.9)	5.8 (1.0)**
n-3 PUFA, % energy	0.7 (0.2)	1.0 (0.3)	1.2 (0.3)**	0.8 (0.3)	1.0 (0.3)	1.0 (0.3)**	0.7 (0.2)	1.0 (0.3)	1.1 (0.3)**
n-6 PUFA, % energy	2.8 (0.7)	3.8 (0.7)	4.7 (0.8)**	3.1 (0.9)	3.9 (0.9)	4.2 (0.9)**	2.9 (0.8)	3.8 (0.7)	4.6 (0.8)**

	PUFA			n-3 PUFA			n-6 PUFA		
	Q1 (low)	Q3	Q5 (high)	Q1 (low)	Q3	Q5 (high)	Q1 (low)	Q3	Q5 (high)
Age, years	56.3 (9.7)	55.0 (9.4)	55.9 (9.1)	55.6 (9.8)	55.0 (9.4)	56.4 (8.9)*	56.5 (9.6)	55.0 (9.4)	55.9 (9.1)*
Family history of diabetes, %	11.2	11.9	9.3**	12.0	11.8	9.2	11.0	12.1	10.1**
Family history of hypertension, %	33.9	36.9	36.5*	34.8	37.8	37.0	34.7	36.7	36.8
Current smoker, %	6.5	3.5	1.7**	5.7	3.9	1.9**	6.4	3.3	1.8**
Current drinker, %	29.5	24.6	20.8**	30.4	23.4	22.4**	30.0	24.7	21.0**
BMI, kg/m^2	22.9 (6.3)	22.8 (2.9)	22.9 (2.9)	22.7(3.0)	22.8 (2.9)	23.0 (3.0)**	22.9 (6.3)	22.7 (2.9)	22.9 (2.9)
BMI ≥25 kg/m^2, %	21.4	19.0	22.2	19.7	20.5	23.0	21.9	18.9	21.9
Exercise ≥ 5 h/week, %	4.6	3.5	5.1**	3.8	4.0	5.7**	4.8	3.5	5.2**
Walking ≥ 0.5 h/week, %	89.2	86.9	86.2**	88.1	88.4	85.6**	89.3	87.2	86.7**
Energy intake, kcal	1529 (396)	1385 (333)	1547(384)**	1533 (383)	1393 (347)	1521 (375)**	1525 (396)	1384 (331)	1544(385)**
Carbohydrate, % energy	69.5 (7.1)	62.6 (5.2)	56.7 (5.3)**	68.7 (7.0)	62.7 (5.6)	57.0 (5.6)**	69.0 (7.5)	62.5 (5.4)	57.1 (5.5)**
Total protein, % energy	12.0 (1.6)	14.9 (1.4)	17.2 (1.9)**	12.0 (1.5)	14.8 (1.2)	17.5 (1.8)**	12.3 (1.9)	14.9 (1.7)	16.8 (1.9)**
Total fat, % energy	15.2 (3.8)	20.8 (3.6)	25.0 (3.7)**	16.5 (4.7)	20.7 (4.0)	24.1 (4.0)**	15.4 (4.0)	20.9 (3.6)	24.9 (3.8)**
SFA, % energy	5.1 (1.8)	6.5 (1.8)	7.2 (1.6)**	5.6 (2.1)	6.5 (1.8)	6.9 (1.6)**	5.1 (1.8)	6.6 (1.8)	7.2 (1.6)**
MUFA, % energy	4.9 (1.4)	6.7 (1.4)	8.1 (1.5)**	5.3 (1.7)	6.7 (1.5)	7.8 (1.6)**	4.9 (1.4)	6.7 (1.4)	8.1 (1.5)**
PUFA, % energy	3.2 (0.5)	4.7 (0.2)	6.3 (0.7)**	3.5 (0.8)	4.8 (0.8)	6.0 (0.9)**	3.2 (0.6)	4.7 (0.3)	6.3 (0.7)**
n-3 PUFA, % energy	0.6 (0.2)	0.9 (0.2)	1.3 (0.3)**	0.6 (0.1)	0.9 (0.1)	1.4 (0.2)**	0.7 (0.3)	0.9 (0.3)	1.2 (0.3)**
n-6 PUFA, % energy	2.5 (0.5)	3.8 (0.3)	5.1 (0.6)**	2.9 (0.7)	3.9 (0.7)	4.5 (0.9)**	2.5 (0.4)	3.8 (0.2)	5.1 (0.6)**

All values are mean (SD) or percentages.

[a]Total fat and fatty acid levels were adjusted for energy intake using the nutrient residual model.

P-trend was calculated using the Mantel-Haenszel chi-squared test for categorical variables and linear regression analysis for continuous variables, with the median intake in each quintile category of total fat and fatty acids intakes.

*<0.05, **<0.01

Participants with missing information were excluded (BMI: n = 408; smoking status: n = 928; drinking status: n = 462; sports information: n = 338; walking information: n = 430).

2.3.2. The association between total fat and fatty acids and incidence of type 2 diabetes

The table presented in Table 9 (men) and 10 (women) displays the OR and 95% CI for type 2 diabetes based on total fat and fatty acids intakes for both men and women. For men, the multivariable-adjusted OR of incident type 2 diabetes for the highest versus lowest quintiles was 0.58 (95% CI, 0.37, 0.90; p-trend = 0.037) for total fat, 0.78 (95% CI 0.51, 1.21; p-trend = 0.120) for SFA, 0.55 (95% CI 0.35, 0.86; p-trend = 0.019) for MUFA, 0.61 (95% CI 0.39, 0.96; p-trend = 0.059) for PUFA, 0.64 (95% CI 0.42, 0.99; p-trend = 0.111) for n-3 PUFA, and 0.70 (95% CI 0.45, 1.09; p-trend = 0.115) for n-6 PUFA, indicating that total fat, MUFA, PUFA, and n-3 PUFA were inversely associated with type 2 diabetes. For women, total fat and fatty acids intakes were not significantly associated with type 2 diabetes.

Table 9. OR and 95% CI of type 2 diabetes according to quintiles of energy-adjusted[a] total fat and fatty acids intakes (men)

	Q1 (low)	Q2	Q3	Q4	Q5 (high)	P for trend[b]
Total fat, g/day	<25.34	25.34-30.31	30.32-34.45	34.46-40.05	>40.05	
No of participants	1408	1409	1409	1409	1409	
No of cases	61	44	50	51	41	
Model 1	1.00 (reference)	0.72 (0.48, 1.07)	0.82 (0.56, 1.21)	0.81 (0.55, 1.20)	**0.66 (0.43, 0.995)**	0.102
Model 2	1.00 (reference)	0.72 (0.48, 1.08)	0.78 (0.52, 1.17)	0.79 (0.53, 1.19)	**0.58 (0.37, 0.90)**	**0.037**
SFA, g/day	<7.12	7.12-8.90	8.91-10.50	10.51-12.57	>12.57	
No of participants	1408	1409	1409	1409	1409	
No of cases	52	51	57	39	48	
Model 1	1.00 (reference)	1.00 (0.67, 1.49)	1.11 (0.75, 1.63)	0.73 (0.48, 1.13)	0.88 (0.59, 1.33)	0.289
Model 2	1.00 (reference)	0.98 (0.66, 1.47)	1.07 (0.72, 1.59)	0.70 (0.45, 1.08)	0.78 (0.51, 1.21)	0.120
MUFA, g/day	<7.79	7.79-9.42	9.43-10.94	10.95-12.89	>12.89	
No of participants	1408	1409	1409	1409	1409	
No of cases	58	50	45	55	39	
Model 1	1.00 (reference)	0.86 (0.58, 1.27)	0.77 (0.52, 1.15)	0.92 (0.63, 1.36)	**0.65 (0.43, 0.99)**	0.084
Model 2	1.00 (reference)	0.83 (0.56, 1.24)	0.74 (0.49, 1.11)	0.86 (0.58, 1.28)	**0.55 (0.35, 0.86)**	**0.019**
PUFA, g/day	<6.19	6.19-7.40	7.41-8.45	8.46-9.73	>9.73	
No of participants	1408	1409	1409	1409	1409	
No of cases	66	47	44	50	40	
Model 1	1.00 (reference)	0.71 (0.48, 1.05)	**0.66 (0.44, 0.99)**	0.78 (0.52, 1.16)	**0.62 (0.40, 0.96)**	0.061
Model 2	1.00 (reference)	0.72 (0.48, 1.07)	0.66 (0.44, 1.00)	0.77 (0.51, 1.16)	**0.61 (0.39, 0.96)**	0.059
n-3 PUFA, g/day	<1.13	1.13-1.38	1.39-1.65	1.66-1.99	>1.99	
No of participants	1408	1409	1409	1409	1409	
No of cases	63	38	55	46	45	
Model 1	1.00 (reference)	**0.60 (0.40, 0.91)**	0.88 (0.60, 1.29)	0.74 (0.50, 1.10)	0.73 (0.49, 1.10)	0.282
Model 2	1.00 (reference)	**0.59 (0.39, 0.90)**	0.87 (0.59, 1.28)	0.70 (0.46, 1.06)	**0.64 (0.42, 0.99)**	0.111
n-6 PUFA, g/day	<4.95	4.95-5.94	5.95-6.80	6.81-7.84	>7.84	
No of participants	1408	1409	1409	1409	1409	
No of cases	49	45	52	47	54	
Model 1	1.00 (reference)	**0.64 (0.43, 0.95)**	0.79 (0.54, 1.17)	**0.59 (0.39, 0.91)**	0.69 (0.45, 1.05)	0.088
Model 2	1.00 (reference)	**0.65 (0.43, 0.98)**	0.80 (0.54, 1.20)	**0.60 (0.38, 0.92)**	0.70 (0.45, 1.09)	0.115

Bold p values are statistically significant (p<0.05). Abbreviations: Q, quintile.
The lowest quintiles of total fat and fatty acids intakes were used as the reference group in the analysis. Model 1 was adjusted for age and stratified jointly according to areas (Hokkaido, Tohoku, Kanto, Chubu, Kinki, Chugoku, and Kyusyu). Model 2 was additionally adjusted for family history of diabetes (yes, no); family history of hypertension (yes, no); smoking status (never, former smoker, current smoker); BMI (<18.5, 18.5–24.9, 25.0–30.0, >30.0 kg/m^2); walking hours (almost none, daily 0.5, 0.6–0.9, ≥1.0 h); hours of exercise (almost none, weekly 1–2, 3–4, and ≥5 h); alcohol consumption habit (never, former drinker, current drinker); energy intake (kcal, continuous); and carbohydrate (g/day; continuous).
[a]Total fat and fatty acids intakes were adjusted for energy intake using the nutrient residual model.
[b]The P value for linear trend was calculated using a continuous variable of total fat and fatty acids intakes assigning the median values in each quartile.

Table 10. OR and 95% CI of type 2 diabetes according to quintiles of energy-adjusted[a] total fat and fatty acids intakes (women)

	Q1 (low)	Q2	Q3	Q4	Q5 (high)	P for trend[b]
Total fat, g/day	<26.75	26.75-31.06	31.07-34.78	34.79-39.25	>39.25	
No of participants	2408	2409	2409	2409	2409	
No of cases	61	47	47	41	46	
Model 1	1.00 (reference)	0.76 (0.51, 1.12)	0.77 (0.52, 1.14)	0.67 (0.44, 1.01)	0.76 (0.51, 1.14)	0.144
Model 2	1.00 (reference)	0.72 (0.47, 1.11)	0.76 (0.48, 1.21)	0.70 (0.41, 1.18)	0.80 (0.43, 1.51)	0.455
SFA, g/day	<7.68	7.68-9.36	9.37-10.83	10.84-12.53	>12.53	
No of participants	2408	2409	2409	2409	2409	
No of cases	53	58	43	44	44	
Model 1	1.00 (reference)	1.11 (0.76, 1.62)	0.82 (0.54, 1.24)	0.85 (0.56, 1.29)	0.82 (0.54, 1.25)	0.182
Model 2	1.00 (reference)	1.12 (0.75, 1.69)	0.85 (0.53, 1.34)	0.93 (0.57, 1.54)	0.93 (0.53, 1.65)	0.643
MUFA, g/day	<8.34	8.34-9.85	9.86-11.19	11.20-12.82	>12.82	
No of participants	2408	2409	2409	2409	2409	
No of cases	59	55	40	46	42	
Model 1	1.00 (reference)	0.95 (0.65, 1.38)	0.68 (0.45, 1.03)	0.78 (0.53, 1.17)	0.73 (0.49, 1.11)	0.084
Model 2	1.00 (reference)	0.86 (0.57, 1.30)	0.65 (0.40, 1.04)	0.73 (0.45, 1.21)	0.68 (0.37, 1.25)	0.181
PUFA, g/day	<6.16	6.16-7.17	7.18-8.06	8.07-9.15	> 9.15	
No of participants	2408	2409	2409	2409	2409	
No of cases	54	46	47	54	41	
Model 1	1.00 (reference)	0.85 (0.57, 1.28)	0.90 (0.60, 1.36)	1.05 (0.70, 1.57)	0.80 (0.51, 1.25)	0.585
Model 2	1.00 (reference)	0.87 (0.57, 1.34)	0.96 (0.62, 1.51)	1.16 (0.72, 1.85)	0.91 (0.51, 1.60)	0.899
n-3 PUFA, g/day	<1.11	1.11-1.35	1.36-1.60	1.61-1.91	>1.91	
No of participants	2408	2409	2409	2409	2409	
No of cases	55	44	48	54	41	
Model 1	1.00 (reference)	0.81 (0.54, 1.22)	0.93 (0.62, 1.38)	1.05 (0.71, 1.55)	0.78 (0.51, 1.20)	0.557
Model 2	1.00 (reference)	0.80 (0.52, 1.22)	0.88 (0.58, 1.36)	1.05 (0.67, 1.63)	0.75 (0.45, 1.28)	0.608
n-6 PUFA, g/day	<4.90	4.90-5.74	5.75-6.46	6.47-7.32	>7.32	
No of participants	2408	2409	2409	2409	2409	
No of cases	57	47	43	47	48	
Model 1	1.00 (reference)	0.83 (0.55, 1.23)	0.77 (0.51, 1.17)	0.85 (0.56, 1.29)	0.88 (0.57, 1.35)	0.617
Model 2	1.00 (reference)	0.86 (0.57, 1.31)	0.83 (0.53, 1.29)	0.95 (0.60, 1.51)	1.01 (0.60, 1.70)	0.889

Bold p values are statistically significant (p<0.05).
Abbreviations: Q, quintile.
The lowest quintiles of total fat and fatty acids intakes were used as the reference group in the analysis. Model 1 was adjusted for age and stratified jointly according to areas (Hokkaido, Tohoku, Kanto, Chubu, Kinki, Chugoku, and Kyusyu). Model 2 was additionally adjusted for family history of diabetes (yes, no); family history of hypertension (yes, no); smoking status (never, former smoker, current smoker); BMI (<18.5, 18.5–24.9, 25.0–30.0, >30.0 kg/m^2); walking hours (almost none, daily 0.5, 0.6–0.9, ≥1.0 h); hours of exercise (almost none, weekly 1–2, 3–4, and ≥5 h); alcohol consumption habit (never, former drinker, current drinker); energy intake (kcal, continuous); and carbohydrate (g/day; continuous).
[a]Total fat and fatty acids intakes were adjusted for energy intake using the nutrient residual model.
[b]The P value for linear trend was calculated using a continuous variable of total fat and fatty acids intakes assigning the median values in each quartile.

2.4. Discussion

The present study analyzed the association between total fat and fatty acids intakes and the risk of type 2 diabetes in Japanese adults. The results of this study indicated that total fat, MUFA, PUFA, and n-3 PUFA intakes were inversely associated with type 2 diabetes in Japanese men but not in women. SFA and n-6 PUFA intakes were not associated with type 2 diabetes in either sex. In women, total fat and fatty acids intakes were not significantly associated with type 2 diabetes. Given the large difference in OR for the association between total fat, MUFA, PUFA, and n-3 PUFA and type 2 diabetes in the Q1 and Q2-5 group of men and the fact that OR of Q1-Q5 is not clearly linear, the lowest total fat, MUFA, PUFA, and n-3 PUFA intakes in men may be at a risk of type 2 diabetes, but higher intake itself is not associated with a reduced risk.

For people over 20 and over in Japan, the number of diabetes cases is rising (Ministry of Health, Labor and Welfare of Japan). Also, intakes of total fat and fatty acids other than n-3 PUFA are increasing (Ministry of Health, Labor and Welfare of Japan). However, the present study found higher intakes of total fat and all fatty acids were not associated with higher risk of type 2 diabetes. Thus, in Japan, total fat and fatty acids intakes may not be a significant contributor to the incidence of type 2 diabetes.

The present study's results regarding total fat, PUFA, and n-3 PUFA intakes in men were inconsistent with previous meta-analyses results (de et al, 2015; Alhazmi et al, 2012; Zhou et al, 2012; Wu et al, 2012; Neuenschwander et al, 2020) that includes studies mainly conducted in non-Asia. On the contrary, the results of two studies conducted in Asia (Brostow et al, 2011; Ha et al, 2019), which were included in the abovementioned meta-analyses (Neuenschwander et al, 2020) are consistent with the results of the present study. This difference may be attributed to the fact that Asians have a lower total fat intake (Dehghan et al, 2017; Zhou et al, 2003) and higher intakes of fish rich in n-3 PUFA and n-3 PUFA than non-Asians (fish intake in 2013: Japan, 48.60 kg/capita/year; the US, 21.51 kg/capita/year; United Kingdom, 20.76 kg/capita/year; n-3 PUFA: Japan, 1.3% energy in men, 1.4% energy in women; the US, 0.7% energy in men, 0.7% energy in women; United Kingdom, 0.7% energy in men, 0.8% energy in women) (Tsugane, 2021). Although it is believed that n-3 PUFA may decrease the risk of developing diabetes by modulating insulin sensitivity in phospholipid membranes (Borkman et al, 1993), the detailed reason for the difference in association of n-3 PUFA and type 2 diabetes between Asia and non-Asia is unknown.

A previous cross-sectional study showed a favorable association between MUFA and β-cell insulin secretion (Rojo-Martínez et al, 2006). Additionally, a previous cohort study reported that increased intake of MUFA is associated with better β-cell function (den et al, 2019). This is because intake of MUFA preserves or even enhances β-cell proliferation and has as an anti-apoptotic effect (Morgan et al, 2008). The present study indicated that MUFA intake is associated with a reduced risk of type 2 diabetes in only men, a finding that is in line with those of the abovementioned previous study (Morgan et al, 2008). On the other hand, a previous meta-analysis indicated that MUFA intake is not associated with the risk of type 2 diabetes (Neuenschwander et al, 2020). The cause for the discrepancy between the results of the present study and those of this previous meta-analysis (Neuenschwander et al, 2020) are unknown. Therefore, further research is needed to clarify the relationship between MUFA intake and the risk of type 2 diabetes.

The present study in men and women indicated that n-6 PUFA and SFA intakes were not associated with the risk of type 2 diabetes. This finding is consistent with those of a previous meta-analysis (Neuenschwander et al, 2020). In addition, experimental evidence suggests that n-6 PUFA is associated with favorable insulin sensitivity, therefore having protective effect against the development of type 2 diabetes (Maki et al, 2018). Conversely, in vitro experimental data has demonstrated that SFA induces insulin resistance (Boden et al, 1997). Thus, although n-6 PUFA and SFA have mechanisms associated with the reduction or increase in the risk of developing diabetes, they may not affect the risk of diabetes in the amounts habitually consumed by humans.

In the present study, there are sex-specific differences in the associations between intakes of total fat and most of fatty acids and the risk of type 2 diabetes, and total fat, MUFA, PUFA, and n-3 PUFA intakes were associated with a lower risk of type 2 diabetes in men but not women. This sex difference could be considered from two possibilities. First, this difference may be partly explained by variations in the incidence of type 2 diabetes between men and women (men: 3.5%; women: 2.0%). Second, in the present study in the baseline 1988-90, women were more likely than men to be full-time homemakers or out of work (full-time homemakers: 31.4% and out of work: 16.2% in women; full-time homemakers: 0.1% and out of work: 14.9% in men). Thus, women are more likely than men to have not received the health check at work and, therefore, may be less accurate in measuring the incidence of diabetes than men.

As for strengths, based on a validated FFQ and controlling for potential confounding factors, this study used a large sample of the community-based population.

Some limitations have to be taken into account. First, because all diagnoses were self-reported, some misclassification of the diagnosis of type 2 diabetes was unavoidable. Nevertheless, the self-reported type 2 diabetes diagnoses were validated, and the results showed moderate sensitivity (70% for men and 75% for women) and specificity (95% for men and 98% for women) (Iso et al, 2006). Second, it is important to consider that the dietary intake was only measured once at the baseline study, which may not have fully captured the long-term intake data. Third, even though the present study had a prospective design, there is a concern about reverse causation due to the short follow-up period of five years. At the baseline study, some participants may have already had prediabetes and altered their diet accordingly. In addition, this study could not exclude participants who had undiagnosed diabetes or prediabetes because JACC Study did not gather information on their blood glucose levels at the baseline study. Thus, in the present study, part of the incidence of type 2 diabetes may be substituted for prevalence at baseline. Fourth, this study results in the late 1980s may not be applicable to the Japanese population in 2024 because diet habit in Japan have changed (1990 v. 2020; energy 2026 kcal v. 1903 kcal, carbohydrate 59.2% energy v. 56.3% energy, total fat 25.3% energy v. 28.6% energy, fish 95.3 g v. 64.1 g, meat 71.2 g v. 103.0 g, and oil 17.6 g v. 11.2 g) (Ministry of Health, Labor and Welfare of Japan). On the contrary, the results are more likely applicable to populations close to their eating habits in 1990. Fifth, because diet assessment was self-reported using FFQ, misclassification may be conduct. However, the FFQ validation study compared to 12 days of weighted dietary records showed moderate Spearman rank correlation coefficients of 0.46 for total fat, 0.50 for SFA, 0.36 for MUFA, 0.15 for PUFA, 0.21 for n-3 PUFA, 0.16 for n-6 PUFA, 0.24 for total protein, 0.31 for animal protein, 0.51 for animal fat, and 0.34 for vegetable fat (Date et al, 2005). Sixth, only data from one-third of the eligible participants was collected due to limitations in the 5-year follow-up survey, which was conducted in specific baseline study areas and not all of them. However, there were no significant differences in the characteristics of the participants, including age, BMI, and other factors, between those who responded to the 5-year survey and those who did not (Eshak et al, 2019). Finally, the present study cannot rule out the possibility of residual confounding factors.

In summary, higher intakes of total fats, MUFA, PUFA, and n-3 PUFA were inversely associated with type 2 diabetes among Japanese men. In women, total fat and fatty acids were not significantly associated with type 2 diabetes.

Chapter 3: Association between low carbohydrate diet score and incidence of type 2 diabetes among Japanese adults: the JACC study

3.1. Introduction

Review study in Chapter 1 revealed that, among Asians such as Japanese, further research is needed to investigate the relationship between a low carbohydrate diet score and type 2 diabetes.

As shown in overall introduction, carbohydrates are the primary nutrient for post-prandial hyperglycemia and insulin secretion, and fats are classified as SFA, MUFA, and PUFA and it has been reported that different types of fatty acids may affect insulin action. On the other hand, as shown in chapter 1, a previous meta-analysis reported that low carbohydrate diet score was not associated with the incidence of diabetes. Most of the studies included in this meta-analysis were conducted in non-Asians.

Previous two studies reported that Asians have a higher carbohydrate intake and a lower fat intake compared to non-Asians (Table 11) (Dehghan et al, 2017; Zhou et al, 2003). In addition, Asians have lower insulin secretory capacity compared to non-Asians (Kadowaki et al, 1984). Thus, the results of the previous meta-analysis study may not apply to Asians such as Japan.

Table 11. Comparison of energy from carbohydrate and fat between Asias and non-Asias

Reference	Asia (energy from carbohydrate)	Non-Asia (energy from carbohydrate)
Zhou et al, 2003	Japan (men): 52.3% energy China (men): 61.8% energy Japan (women): 56.2% energy China (women): 68.1% energy	Japan (men): 46.6% energy China (men): 48.4% energy Japan (women): 48.3% energy China (women): 50.5% energy
Dehghan et al, 2017	China: 67.0% energy South Asia: 65.4% energy	Europe and North America: 52.4%
Reference	**Asia (energy from total fat)**	**Non-Asia (energy from total fat)**
Zhou et al, 2003	Japan (men): 23.7% energy China (men): 20.5% energy Japan (women): 26.1% energy China (women): 19.5% energy	United Kingdom (men): 33.0% energy the US (men): 33.3% energy United Kingdom (women): 32.5% energy the US (women): 32.6% energy
Dehghan et al, 2017	China: 17.7% energy South Asia: 20.5% energy	Europe and North America: 30.5% energy

Therefore, in this chapter, the aim was to clarify the association between low carbohydrate diet score and type 2 diabetes risk in Japanese adults in Asia using JACC Study data.

3.2. Methods

3.2.1. Study design and population

This research was conducted using JACC study data (Tamakoshi et al, 2005; Tamakoshi et al, 2013). In brief, the JACC study was conducted from 1988 through 1990 with participants aged 40–79 years and was a multicenter collaborative study in which 24 institutions participated. For other detail background to the research, please study design and population in chapter 2.

3.2.2. Ethical issues

Please refer to ethical issues in chapter 2.

3.2.3. Assessment of dietary intake

The participants were asked to report their consumption of 40 food and drink items over the past year in FFQ (Date et al, 2005). Please refer to assessment of dietary intake in chapter 2 for details on FFQ content and validity study methods.

The FFQ-estimated intakes of these nutrients were correlated with those estimated from the dietary records of the validation study (Total protein: 0.24, animal protein: 0.31, total fat: 0.46, animal fat: 0.51, and vegetable fat: 0.34, respectively) (Date et al, 2005). The validation study to evaluate of dietary intake over a one-year period using four three-day weighted dietary records of 85 participants (eight men and 77 women) was used as a reference to estimate size of each meal portion and obtain data on the validity of the FFQ-estimated intakes.

Carbohydrate (% energy), total protein (% energy), animal protein (% energy), vegetable protein (% energy), total fat (% energy), animal fat (% energy), and vegetable fat (% energy) were calculated as follows by applying Atwater factors.

Total protein (% energy) = (4 (kcal) × total protein(g)/total energy (kcal)) × 100
Animal protein (% energy) = (4 (kcal) × animal protein(g)/total energy (kcal)) × 100
Vegetable protein (% energy) = (4 (kcal) × vegetable protein(g)/total energy (kcal)) × 100
Total fat (% energy) = (9 (kcal) × total fat(g)/total energy (kcal)) ×100
Animal fat (% energy) = (9 (kcal) × animal fat(g)/total energy (kcal)) ×100
Vegetable fat (% energy) = (9 (kcal) × vegetable fat(g)/total energy (kcal)) ×100
Carbohydrate (% energy) = 100 – ((total protein (% energy) + total fat (% energy))

To calculate total protein, animal protein, total fat, animal fat, and vegetable fat intakes, the fourth revised version of standard tables of Food Composition in Japan was used.

3.2.4. Calculation of low carbohydrate diet scores

The study calculated three different low carbohydrate diet scores: the overall low carbohydrate diet score, the animal low carbohydrate diet score, and the vegetable low carbohydrate diet score. The score calculations were based on a previous study (Halton et al, 2006).

For the overall low carbohydrate diet score, the study participants were divided into eleven categories based on the percentages of energy from carbohydrates, total protein, and total fat. This division was done separately for men and women. The carbohydrate categories were scored from 10 to 0 points, with the highest intake receiving 10 points and the lowest intake receiving 0 points. Conversely, the total protein and total fat categories were scored from 0 to 10 points, with the highest intake receiving 10 points and the lowest intake receiving 0 points. The overall low carbohydrate diet score ranged from 0 to 30, with the carbohydrates, proteins, and fats intake points summed up to obtain the score. A higher score indicated that a higher proportion of energy was derived from total fat and total protein, and a lower proportion of energy was derived from carbohydrates. In the same way, we calculated the animal low carbohydrate diet score based on the proportion of energy obtained from animal fat, animal protein, and carbohydrates. Similarly, we derived the vegetable low carbohydrate diet score from the proportion of energy derived from vegetable protein, vegetable fat, and carbohydrates. Table 12 outlines the criteria used to determine the scores for low carbohydrate diets.

Table 12. Criteria for determining the low carbohydrate diet score

Points	Carbohydrate	Total protein	Total fat	Animal protein	Animal fat	Vegetable protein	Vegetable fat
			Percentage of energy				
			Men				
0	>78.72	<10.03	<11.12	<3.63	<3.48	<5.23	<4.83
1	76.03-78.72	10.03-11.02	11.12-12.79	3.63-4.39	3.48-4.53	5.23-5.80	4.83-5.68
2	73.94-76.02	11.03-11.73	12.80-14.16	4.40-4.92	4.54-5.36	5.81-6.20	5.69-6.30
3	72.30-73.93	11.74-12.29	14.17-15.30	4.93-5.41	5.37-6.08	6.21-6.50	6.31-6.85
4	70.76-72.29	12.30-12.84	15.31-16.31	5.42-5.88	6.09-6.72	6.51-6.77	6.86-7.39
5	69.22-70.75	12.85-13.37	16.32-17.39	5.89-6.39	6.73-7.44	6.78-7.04	7.40-7.89
6	67.56-69.21	13.38-13.95	17.40-18.53	6.40-6.88	7.45-8.17	7.05-7.34	7.90-8.43
7	65.67-67.55	13.96-14.60	18.54-19.85	6.89-7.47	8.18-9.00	7.35-7.66	8.44-9.08
8	63.23-65.66	14.61-15.43	19.86-21.52	7.48-8.23	9.01-10.09	7.67-8.06	9.09-9.85
9	59.61-63.22	15.44-16.75	21.53-23.98	8.24-9.36	10.10-11.82	8.07-8.62	9.86-10.99
10	<59.61	>16.75	>23.98	>9.36	>11.82	>8.62	>10.99
			Women				
0	>72.55	<12.56	<14.57	<4.86	<4.75	<6.35	<6.11
1	69.22-72.55	12.56-13.57	14.57-16.91	4.86-5.80	4.75-6.21	6.35-6.76	6.11-7.14
2	66.99-69.21	13.58-14.30	16.92-18.46	5.81-6.47	6.22-7.25	6.75-7.06	7.15-7.93
3	65.23-66.98	14.31-14.89	18.47-19.70	6.48-7.04	7.26-8.08	7.07-7.34	7.94-8.54
4	63.57-65.22	14.90-15.42	19.71-20.83	7.05-7.57	8.09-8.87	7.35-7.61	8.55-9.13
5	62.10-63.56	15.43-15.91	20.84-21.91	7.58-8.08	8.88-9.63	7.62-7.87	9.14-9.67
6	60.63-62.09	15.92-16.46	21.92-22.94	8.09-8.59	9.64-10.40	7.88-8.15	9.68-10.21
7	59.02-60.62	16.47-17.04	22.95-24.11	8.60-9.21	10.41-11.25	8.16-8.45	10.22-10.82
8	57.11-59.01	17.05-17.75	24.12-25.53	9.22-9.95	11.26-12.34	8.46-8.80	10.83-11.52
9	54.05-57.10	17.76-18.81	25.54-27.66	9.96-11.07	12.35-13.84	8.81-9.31	11.53-12.59
10	<54.05	>18.81	>27.66	>11.07	>13.84	>9.31	>12.59

3.2.5. Assessment of diabetic status

Please refer to assessment of diabetic status in chapter 2.

3.2.6. Assessment of other factors

Please refer to assessment of other factors in chapter 2.

3.2.7. Statistical analysis

Participants were classified into quintiles of the three low carbohydrate diet scores according to sex. Using the lowest quintile of the three low carbohydrate diet scores as a reference, logistic regression analyses were used to estimate the OR and 95% CI of incident type 2 diabetes. The multivariable model was adjusted for age (continuous); family history of diabetes (yes, no); family history of hypertension (yes, no); smoking status (never, former smoker, current smoker); BMI (<18.5, 18.5–24.9, 25.0–30.0, >30.0 kg/m^2); walking hours (almost none, daily 0.5, 0.6–0.9, ≥1.0 h); exercise hours (almost none, weekly 1–2, 3–4, ≥5 h); alcohol habit (never, former drinker, current drinker); and energy intake (continuous). Tests for trends were conducted using the median value for each quintile of the three low carbohydrate diet scores as a continuous variable. An indicator variable for missing data was created for each covariate. All analyses were conducted separately according to sex because Japanese people have different dietary habits depending on sex (2118 kcal, carbohydrate: 274.6 g, total protein: 77.7 g, total fat: 66.4 g in men; 1709 kcal, carbohydrate: 224.6 g, total protein: 65.7 g, total fat: 56.7 g in women). A significance level for a two-sided P value <0.05 using the SAS 9.4 software (SAS Institute Inc., Cary, NC, USA) was applied for all statistical analyses.

3.3. Results

Several criteria were used to exclude certain participants from the study. These included living areas that were not surveyed for dietary information (n = 24,184); missing dietary data (n = 24,614); reported extreme dietary intakes (<500 kcal or >3500 kcal) (n = 171); living areas that were not surveyed for diabetes evaluation after 5 years of follow-up (n = 5,529); medical histories of diabetes, cancer, or myocardial infarction at baseline (n = 8,838); and participants who had not provided data on their history of diabetes at the 5-year survey (n = 28,165). After applying these criteria, 19,084 eligible patients (7,052 men and 12,032 women) were included in the analysis.

3.3.1. The baseline characteristics of the participants

During the 5-year study period, 490 individuals developed type 2 diabetes, which amounts to 2.6% of the total participants. Among these, 247 (3.5%) were men and 243 (2.0%) were women. Table 13 (men) and 14 (women) displays the characteristics of the study participants according to the quintile of the low carbohydrate diet scores. Men and women who had the highest score of the three low carbohydrate diet scores were generally more likely to be current smokers compared to those with the lowest score. Among men, those with the highest score of the three low carbohydrate diet scores were older than those with the lowest score. Conversely, among women, those with the highest overall and animal low carbohydrate diet scores were younger than those with the lowest scores.

Table 13. Baseline characteristics of participants according to quintile categories of low carbohydrate diet score (men)

	Overall low carbohydrate diet score				**Animal low carbohydrate diet score**				**Vegetable low carbohydrate diet score**			
	Q1 (low)		**Q5 (high)**		**Q1 (low)**		**Q5 (high)**		**Q1 (low)**		**Q5 (high)**	
	Mean or n	SD or %	Mean or n	SD or %	Mean or n	SD or %	Mean or n	SD or %	Mean or n	SD or %	Mean or n	SD or %
Median score (range)	2 (0-5)		28 (25-30)		3 (0-6)		28 (25-30)		4 (0-7)		26 (23-30)	
Age, years	54.5	9.3	58.0	9.8	54.9	9.4	57.6	9.9	54.0	9.2	57.6	9.8
Family history of diabetes, n (%)	114	8.3	138	10.1	128	8.5	136	10.5	134	8.9	167	11.2
Family history of hypertension, n (%)	493	35.9	462	33.8	549	36.4	433	33.5	548	36.6	526	35.3
Current smoker, n (%)	798	58.1	590	43.2	844	55.9	588	45.6	891	59.4	634	42.5
Current drinker, n (%)	1233	89.7	811	59.3	1303	86.3	820	63.5	1406	93.8	824	55.3
BMI, kg/m^2	22.7	2.6	22.6	4.5	22.7	2.7	22.6	4.5	22.7	2.6	22.6	2.8
Sports ≥ 5 h/week, n (%)	91	6.6	118	8.6	96	6.4	114	8.8	98	6.5	133	8.9
Walking ≥ 0.5 h/week, n (%)	1201	87.4	1200	87.7	1316	87.2	1143	88.5	1302	86.9	1302	87.3
Energy intake, kcal	1810	471	1434	431	1833	473	1431	429	1754	457	1548	467
Carbohydrate, % energy	79.2	2.9	58.8	4.3	78.4	3.4	59.1	4.8	77.4	4.2	61.4	5.5
Total protein, % energy	10.0	1.2	16.9	1.7	10.4	1.4	16.6	1.9	10.5	1.6	16.1	1.9
Animal protein, % energy	3.8	1.1	9.3	1.8	3.7	0.9	9.5	1.6	4.9	1.7	7.8	2.1
Vegetable protein, % energy	6.2	1.2	7.6	1.3	6.7	1.2	7.1	1.3	5.6	0.9	8.3	1.0
Total fat, % energy	10.9	2.0	24.4	3.1	11.2	2.2	24.4	3.3	12.1	2.9	22.5	3.9
Animal fat, % energy	4.1	1.7	11.1	2.9	3.8	1.3	11.9	2.4	5.4	2.4	9.3	3.0
Vegetable fat, % energy	5.4	1.4	10.4	2.2	6.0	1.7	9.7	2.4	5.0	1.1	10.9	1.6
SFA, % energy	3.2	0.8	7.2	1.5	3.2	0.7	7.5	1.4	3.8	1.3	6.3	1.5
MUFA, % energy	3.2	0.7	7.6	1.2	3.3	0.7	7.7	1.1	3.7	1.0	6.8	1.4
PUFA, % energy	3.0	0.7	6.0	1.1	3.3	0.9	5.7	1.3	3.0	0.6	6.1	1.0

Table 14. Baseline characteristics of participants according to quintile categories of low carbohydrate diet score (women)

	Overall low carbohydrate diet score				**Animal low carbohydrate diet score**				**Vegetable low carbohydrate diet score**			
	Q1 (low)		**Q5 (high)**		**Q1 (low)**		**Q5 (high)**		**Q1 (low)**		**Q5 (high)**	
	Mean or n	SD or %	Mean or n	SD or %	Mean or n	SD or %	Mean or n	SD or %	Mean or n	SD or %	Mean or n	SD or %
Median score (range)	2 (0-5)		28 (25-30)		3 (0-6)		27 (24-30)		4 (0-7)		25 (23-30)	
Age, years	56.9	9.7	55.0	9.2	57.3	9.6	54.4	9.2	56.0	9.7	56.2	9.3
Family history of diabetes, n (%)	230	10.0	317	10.4	248	9.8	268	11.1	263	11.3	211	9.7
Family history of hypertension, n (%)	767	33.4	986	36.6	830	32.7	910	37.6	808	34.7	764	35.2
Current smoker, n (%)	139	6.1	56	2.5	136	5.4	72	3.0	152	6.5	44	2.0
Current drinker, n (%)	640	27.9	502	22.5	636	25.1	607	25.1	775	33.3	371	17.1
BMI, kg/m^2	23.0	6.5	22.7	2.9	22.9	3.1	22.6	2.9	23.0	6.4	22.9	3.0
Sports ≥ 5 h/week, n (%)	101	4.4	117	5.3	121	4.8	123	5.1	103	4.4	108	5.0
Walking ≥ 0.5 h/week, n (%)	1999	87.1	1928	86.5	2217	87.4	2111	87.1	2061	88.4	1861	85.8
Energy intake, kcal	1380	380	1302	370	1381	382	1303	360	1331	362	1340	345
Carbohydrate, % energy	73.2	3.6	53.2	3.5	72.3	4.2	54.0	4.0	71.1	5.1	56.1	4.7
Total protein, % energy	12.5	1.3	18.9	1.6	12.9	1.6	18.4	1.8	13.1	1.8	18.0	1.9
Animal protein, % energy	5.0	1.4	11.0	1.8	5.0	1.2	11.0	1.7	6.4	2.0	9.1	2.0
Vegetable protein, % energy	7.5	1.1	7.9	1.3	8.0	1.2	7.5	1.1	6.7	0.7	8.9	0.9
Total fat, % energy	14.3	2.6	27.9	2.7	14.8	2.9	27.5	2.8	15.8	3.6	25.9	3.3
Animal fat, % energy	5.7	2.2	12.9	3.0	5.2	1.8	13.6	2.4	7.4	3.0	10.4	2.9
Vegetable fat, % energy	7.0	1.8	11.4	2.2	7.8	2.3	10.6	2.3	6.2	1.2	12.5	1.6
SFA, % energy	4.3	1.1	8.2	1.4	4.2	0.9	8.4	1.2	5.1	1.5	7.1	1.4
MUFA, % energy	4.3	0.9	8.7	1.1	4.3	0.9	8.7	1.1	4.9	1.3	7.8	1.3
PUFA, % energy	3.8	0.9	6.7	1.1	4.2	1.1	6.2	1.2	3.6	0.7	6.9	0.9

3.3.2. The association between low carbohydrate diet score and type 2 diabetes

The Table 15 (men) and 16 (women) displays the OR and 95% CI for type 2 diabetes based on three low carbohydrate diet scores for both men and women. Upon adjusting for covariates, there is no evidence to suggest that overall, animal low carbohydrate diets scores increase the risk of type 2 diabetes in either sex. The vegetable low carbohydrate diet score shows a significant association with a decreased risk of type 2 diabetes (P for trend = 0.004), with the highest quintile of the score associated with an OR of 0.51 (95% CI: 0.33, 0.77) compared to the lowest quintile in men. This was not the case for women.

Table 15. OR and 95% CI of type 2 diabetes according to quintile categories of low carbohydrate diet score (men)

	Q1 (low)	Q2	Q3	Q4	Q5 (high)	P for trend
Overall low carbohydrate diet score						
Median score (range)	2 (0-5)	8 (6-11)	15 (12-18)	22 (19-24)	28 (25-30)	
No of participants	1375	1333	1607	1371	1367	
No of cases	62	35	55	52	43	
Age adjusted model	1.00 (reference)	**0.57 (0.37, 0.86)**	0.73 (0.51, 1.06)	0.79 (0.54, 1.15)	**0.62 (0.42, 0.92)**	0.139
Multivariable model	1.00 (reference)	**0.58 (0.38, 0.89)**	0.75 (0.51, 1.09)	0.80 (0.54, 1.18)	**0.64 (0.42, 0.99)**	0.213
Animal low carbohydrate diet score						
Median score (range)	3 (0-6)	10 (7-12)	15 (13-17)	21 (18-24)	28 (25-30)	
No of participants	1510	1411	1230	1610	1291	
No of cases	59	38	50	55	45	
Age adjusted model	1.00 (reference)	0.68 (0.45, 1.04)	1.02 (0.70, 1.50)	0.84 (0.58, 1.22)	0.82 (0.55, 1.23)	0.538
Multivariable model	1.00 (reference)	0.68 (0.45, 1.04)	1.03 (0.70, 1.52)	0.84 (0.57, 1.23)	0.83 (0.55, 1.27)	0.591
Vegetable low carbohydrate diet score						
Median score (range)	4 (0-7)	10 (8-12)	15 (13-17)	20 (18-22)	26 (23-30)	
No of participants	1499	1313	1443	1306	1491	
No of cases	75	39	44	47	42	
Age adjusted model	1.00 (reference)	**0.56 (0.38, 0.83)**	**0.57 (0.39, 0.83)**	**0.65 (0.45, 0.95)**	**0.49 (0.33, 0.72)**	**0.001**
Multivariable model	1.00 (reference)	**0.56 (0.38, 0.84)**	**0.59 (0.40, 0.88)**	**0.66 (0.45, 0.97)**	**0.51 (0.33, 0.77)**	**0.004**

Bold p values are statistically significant ($p<0.05$).

The multivariable model was adjusted for age (continuous); family history of diabetes (yes, no); family history of hypertension (yes, no); smoking status (never, former smoker, current smoker); BMI (<18.5, 18.5-24.9, 25.0-30.0, >30.0 kg/m^2); walking hours (almost none, daily 0.5, 0.6–0.9, ≥1.0 h); exercise hours (almost none, weekly 1–2, 3–4, ≥5 h); alcohol habit (never, former drinker, current drinker); and energy intake (continuous).

Table 16. OR and 95% CI of type 2 diabetes according to quintile categories of low carbohydrate diet score (women)

	Q1 (low)	Q2	Q3	Q4	Q5 (high)	P for trend
Overall low carbohydrate diet score						
Median score (range)	2 (0-5)	9 (6-12)	16 (13-18)	21 (19-24)	28 (25-30)	
No of participants	2296	2670	2389	2449	2228	
No of cases	57	54	45	48	39	
Age adjusted model	1.00 (reference)	0.84 (0.58, 1.23)	0.79 (0.53, 1.18)	0.82 (0.56, 1.21)	0.74 (0.49, 1.11)	0.159
Multivariable model	1.00 (reference)	0.83 (0.57, 1.22)	0.85 (0.57, 1.27)	0.90 (0.60, 1.33)	0.78 (0.51, 1.18)	0.348
Animal low carbohydrate diet score						
Median score (range)	3 (0-6)	10 (7-12)	15 (13-17)	20 (18-23)	27 (24-30)	
No of participants	2536	2309	2165	2599	2423	
No of cases	65	45	43	44	46	
Age adjusted model	1.00 (reference)	0.79 (0.54, 1.16)	0.82 (0.55, 1.21)	0.69 (0.47, 1.02)	0.80 (0.54, 1.17)	0.155
Multivariable model	1.00 (reference)	0.80 (0.54, 1.18)	0.86 (0.58, 1.28)	0.76 (0.52, 1.13)	0.84 (0.57, 1.24)	0.325
Vegetable low carbohydrate diet score						
Median score (range)	4 (0-7)	11 (8-13)	16 (14-17)	20 (18-22)	25 (23-30)	
No of participants	2331	2703	2206	2622	2170	
No of cases	60	50	35	56	42	
Age adjusted model	1.00 (reference)	0.74 (0.50, 1.08)	**0.63 (0.41, 0.95)**	0.84 (0.58, 1.21)	0.74 (0.50, 1.11)	0.207
Multivariable model	1.00 (reference)	0.80 (0.54, 1.17)	0.69 (0.45, 1.06)	0.92 (0.63, 1.35)	0.83 (0.55, 1.24)	0.476

Bold p values are statistically significant ($p<0.05$).
The multivariable model was adjusted for age (continuous); family history of diabetes (yes, no); family history of hypertension (yes, no); smoking status (never, former smoker, current smoker); BMI (<18.5, 18.5-24.9, 25.0-30.0, >30.0 kg/m^2); walking hours (almost none, daily 0.5, 0.6–0.9, ≥1.0 h); exercise hours (almost none, weekly 1–2, 3–4, ≥5 h); alcohol habit (never, former drinker, current drinker); and energy intake (continuous).

3.4. Discussion

The present study found that the overall, and animal low carbohydrate diet score was not associated with higher risk of type 2 diabetes in both sexes. In addition, vegetable low carbohydrate diet score was associated with a lower risk of type 2 diabetes in men but not women.

Previous studies in the US have found that a higher animal low carbohydrate diet score is associated with a higher incidence of diabetes (Bao et al, 2016; de et al, 2011). In contrast to these studies, the present study results did not show a positive association between a higher animal low carbohydrate diet score and the incidence of diabetes. This difference may be due to fish and meat intake variations between Japan in the present study and the US in the previous studies (fish: Japan 48.60 kg/capita/year, the US 21.51 kg/capita/year; meat: Japan 49.45 kg/capita/year, the US 115.13 kg/capita/year) (Tsugane, 2021). Deckelbaum et al. (2006) suggested that consumption of n-3 PUFA found in fish may have beneficial effects on insulin resistance and type 2 diabetes (Deckelbaum et al, 2006). This is due to their ability to inhibit inflammatory pathways and suppress the expression of genes associated with lipid metabolism (Deckelbaum et al, 2006). In addition, the intake of red meat containing iron may increase oxidative stress, leading to damage of pancreatic beta cells (Rajpathak et al, 2009). Thus, among Japanese with high fish and low meat intakes, a higher animal low carbohydrate diet score may not lead to a higher risk for diabetes unlike the US. The results in the present study that the animal low carbohydrate diet score did not show a higher type 2 diabetes risk is consistent with the previous study in Japan (Nanri et al, 2015).

The present study revealed that men who followed a high vegetable low carbohydrate diet score had a lower incidence of type 2 diabetes. The reason for this can be attributed to the consumption of a high amount of vegetable fat. Several studies suggest that consuming high amounts of vegetable fat may lower the risk of developing type 2 diabetes (Colditz et al, 1992; Salmerón et al, 2001). Moreover, a previous meta-analysis found that intaking alpha-linolenic acid, found in certain plants, is linked to a lower risk of developing type 2 diabetes (Wu et al, 2012). Another reason is that the lower vegetable low carbohydrate diet score group may have lived healthier lives than the higher group. Because the lower score group had a higher number of current smokers and current drinkers compared to the higher group, unmeasured health-related factors could have influenced the results.

The present study did not find any evidence as a risk between the higher three low carbohydrate diet scores and a higher risk of type 2 diabetes in both sexes. This contradicts the findings of previous studies in the US (Bao et al, 2016; de et al, 2011). The aforementioned difference may be due to not only insulin secretion capacity but also sources of fat intake between the present study in Japanese and previous studies in the US (Bao et al, 2016; de et al, 2011). Asian such as Japanese have impaired insulin secretion (Colditz et al, 1992) and rely more on carbohydrates for energy than non-Asians (Dehghan et al, 2017; Zhou et al, 2003). Individuals in Japan with high scores for a low-carbohydrate diet may not have an increased risk of type 2 diabetes, regardless of their type of protein or fat intake. On the other hand, it is possible that the differences in findings between this study in Japan and previous studies in the US (Bao et al, 2016; de et al, 2011) are due to differences in study design. In the present study, a dietary survey was conducted only at the beginning, while in previous studies in the US, it was conducted once every 4 years (Bao et al, 2016; de et al, 2011; Halton et al, 2008). Moreover, the follow-up period was 5 years in the present studies and 20 years in the previous studies in the US (Bao et al, 2016; de et al, 2011; Halton et al, 2008). Therefore, it is necessary to conduct further long-term follow-up cohort studies among Japanese with multiple dietary surveys.

In the present study, the vegetable low carbohydrate diet score was associated with type 2 diabetes risk reduction among men but not women. This sex difference could be considered from variations in the incidence of type 2 diabetes between men and women, and women may not perceive the incidence of diabetes more accurately than men, as shown in chapter 2.

As for strengths, based on a validated FFQ and controlling for potential confounding factors, this study used a large sample of the community-based population, similar to that shown in chapter 2.

Some limitations are the same as in chapter 2. A further limitation in chapter 3 is that it should be noted that the cutoff values indicated by the low-carbohydrate diet score in the results of this study may not apply to other populations because the low-carbohydrate diet score table varies by population.

In summary, overall, the animal low carbohydrate diet score was not associated with the incidence of type 2 diabetes in both sexes, while the vegetable low carbohydrate diet score was associated with a lower incidence in men. The findings of this study suggest that in populations with high fish and low meat consumption, such as the Japanese, a diet lower in carbohydrates and higher in fat and protein is unlikely to increase the risk of developing type 2 diabetes.

Conclusions

1) Summary

Diabetes mellitus, a metabolic disease, is suspected to be occurred with higher intake of energy-producing nutrients such as carbohydrates and fat. Carbohydrate is the primary nutrient for post-prandial hyperglycemia and insulin secretion. Fat is classified as SFA, MUFA, and PUFA, and different type of fatty acids to affect insulin action. Currently, intakes of carbohydrates and fat have changed; therefore, it is important to examine the association between carbohydrate and fat intakes as exposure factors and the incidence risk of type 2 diabetes.

The author reported the following findings in this thesis:

1. By review study, among Asians such as Japanese, 1) for association with fat and low carbohydrate diet score and type 2 diabetes, further research is needed; 2) for association with carbohydrate, fat, and low carbohydrate diet score and type 2 diabetes, long follow-up periods, larger numbers of participants, and repeated FFQ studies is needed.
2. Among Japanese, higher intakes of total fat, MUFA, PUFA, and n-3 PUFA were inversely associated with type 2 diabetes among men. In women, total fat and fatty acids were not significantly associated with type 2 diabetes (Chapter 2).
3. Among Japanese, the overall, and animal low carbohydrate diet score was not associated with a higher incidence of type 2 diabetes in both sexes (Chapter 3).

2) The significance and implications of the study

Compared to non-Asian countries, carbohydrate energy ratios are higher and fat energy ratios and insulin secretion are lower in Asia; therefore, the results of association between carbohydrate and fat intakes as exposure factors and incidence risk of type 2 diabetes may not be applicable in Asia.

In the present study, a review revealed that studies examining the association of carbohydrate and fat intakes with incidence risk of type 2 diabetes were not enough in Asia, and I conducted studies on these among Japanese. For total fat, MUFA, PUFA, and n-3 PUFA, although no significant associations with type 2 diabetes were found in the meta-analysis, which included many non-Asians, the present study found an inverse association with type 2 diabetes in Japanese men. For low carbohydrate diet score, higher scores were not significant associations with type 2 diabetes in accordance with the meta-analysis, which included many non-Asians.

Therefore, I believe that the present study extends the evidence for diabetes incidence.

3) Future study

As shown in chapter 1, among Asians such as Japanese, for association with carbohydrate, fat, and low carbohydrate diet score and type 2 diabetes, long follow-up periods, larger numbers of participants, and repeated FFQ studies is needed.

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