Dietary Intake and TCF7L2 rs7903146 T Allele Are Associated with Elevated Blood Glucose Levels in Healthy Individuals

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Abstract
Introduction: Type 2 diabetes (T2D) is a leading cause of global mortality with diet and genetics being considered amongst the most significant risk factors. Recently, studies have identified a single polymorphism of the TCF7L2 gene (rs7903146) as the most important genetic contributor. However, no studies have explored this factor in a healthy population and using glycated haemoglobin (HbA1c), which is a reliable long-term indicator of glucose management. This study investigates the association of the genetic polymorphism rs7903146 and dietary intake with T2D risk in a population free of metabolic disease. Methods: T2D risk was assessed using HbA1c plasma concentrations and dietary intake via a validated Food Frequency Questionnaire in 70 healthy participants. Results: T allele carriers had higher HbA1c levels than the CC group (32.4 ± 7.2 mmol/mol vs. 30.3 ± 7.6 mmol/mol, \( p = 0.005 \)). Multiple regression reported associations between diet, genotype and HbA1c levels accounting for 37.1\% of the variance in HbA1c (adj. \( R^2 = 0.371, p < 0.001 \)). The following macronutrients, expressed as a median percentage of total energy intake (TEI) in the risk group, were positively associated with HbA1c concentration: carbohydrate (\( \geq 39\% \) TEI, \( p < 0.005 \); 95\% CI 0.030/0.130) protein (\( \geq 21\% \) TEI, \( p < 0.005 \), 95\% CI 0.034/0.141), monounsaturated (\( \geq 15\% \) TEI \( p < 0.05 \), 95\% CI 0.006/0.163) and saturated fatty acids (\( \geq 13\% \) TEI; \( p < 0.05 \), 95\% CI 0.036/0.188). Conclusion: Carriers of the T allele showed significantly higher levels of HbA1c compared to non-carriers. Dietary intake affected T2D risk to a greater extent than genetic effects of TCF7L2 rs7903146 genotype in a healthy population. The study focus on healthy individuals is beneficial due to the applicability of findings for T2D screening.
huge burdens on healthcare infrastructures and it is estimated that 10% (USD 760 billion) of global health expenditure is spent on diabetes [2].

Physiologically, glucose management depends on appropriate insulin secretion by pancreatic beta cells and normal tissue response to facilitate glucose uptake. In conditions of elevated free fatty acids, peripheral glucose uptake is decreased, and beta-cell function is impaired. These processes promote insulin resistance and elevated blood glucose levels, which lead to development of T2D [3]. High body mass index and adiposity are amongst the main modifiable risk factors for T2D [4]. In addition, physical activity, age, family history, ethnicity, and diet are some of the main risk factors for development of the disease, independent of body weight. Dietary factors that are linked with T2D include sugar sweetened beverages as well as red and processed meat intake. In contrast, consumption of wholegrains is linked to a reduced risk [5]. Consumption of fruit and dairy products has also been associated with a lower risk for T2D but the evidence supporting these associations is less convincing [6].

In addition to dietary risk factors, it has been shown that genetic predispositions are also associated with development of T2D. A recent meta-analysis of genome-wide association studies (GWAS) identified 139 common variants associated with T2D. The most significant variant in this meta-analysis (2,892 cases and 596,424 controls) was rs7903146 in the TCF7L2 gene [7]. Previous meta-analyses also identified rs7903146 as the most significant genetic variant in relation to diabetes [8, 9]. The rs7903146 polymorphism is an intron variant in the TCF7L2 gene with a minor allele frequency of 0.23 in all populations and 0.32 in Europeans [10]. Although the mechanism by which TCF7L2 affects T2D is unclear, it has been suggested that it is involved in the synthesis of glucagon from human endocrine cells in the gut affecting plasma glucagon levels [11, 12]. The importance of rs7903146 in T2D is further increased due to its interactions with diet. Dietary intake of saturated fatty acids (SFA) above 15.5% of total energy intake is associated with impaired insulin sensitivity in the T (minor) allele carriers relative to CC homozygotes [13]. Conversely, adherence to a Mediterranean diet is significantly associated with a lower concentration of fasting plasma glucose in carriers of the T allele [14]. A further study reported reduced insulin secretion in risk-allele carriers who have an omega-6 dietary intake >6% of total energy intake [15].

Studies investigating the associations between rs7903146 and T2D risk have utilised highly variable acute measures, such as fasting plasma glucose [16]. Such measures can be influenced by non-dietary environmental factors, such as stress and physical activity [17]. Glycated haemoglobin (HbA1c) is an alternative biomarker that provides an estimation of an individual’s average blood glucose level for the previous 60–90 days and is less easily influenced by acute environmental factors [17]. A GWAS meta-analysis in T2D reported that HbA1c provides a less volatile measure of T2D risk [18]. Considering the limitations of the existing literature, this study aims to investigate whether dietary intake and rs7903146 genotype contribute to HbA1c levels in healthy adults, focusing on primary prevention of T2D.

Materials and Methods

Participants
Seventy-four Caucasian participants were recruited for this cross-sectional study via social media and the institutional centre for workplace and community health. Participants were required to attend the laboratory, all data for participants were collected between April and July 2019. Participants were required to be adults and self-reported free from metabolic disease and medication affecting HbA1c levels. All participants completed a Food Frequency Questionnaire (FFQ) and Physical Activity Readiness Questionnaire (PAR-Q) and provided a saliva sample. Four volunteers were excluded due to unsuccessful genotyping or incomplete FFQ completion. This study was conducted in accordance with the Declaration of Helsinki and all participants were briefed and informed that they could withdraw at any point and subsequently provided written consent before inclusion. All procedures involving human participants were approved by the St Mary’s University Ethics Committee (SMEC_2018-19_034). The study is registered at https://clinicaltrials.gov/ (reference: NCT04446754).

Anthropometry
Participant height was recorded to the nearest 0.1 cm via a stadiometer. Body weight, fat mass (%), and muscle mass (kg) were measured by bioelectrical impedance analysis (BC-418MA; Tanita, Tokyo, Japan) using a 0.5-kg clothing offset. Waist circumference was measured midway between the iliac crest and lowest rib. Hip circumference was measured over the greater trochanters at their widest points (nearest 0.1 cm).

Food Frequency Questionnaire
Dietary intake was estimated using the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk validated FFQ and analysed using the FETA platform [19]. The FFQ includes a 130-item list including food groups, individual foods or combinations of individual foods. Participants were asked to select from the nine frequency consumption categories for each item for the preceding year. The questionnaire requires additional information on foods listed in part 1, such as type of milk and cereal consumption, intake of visible fat and type of fat for frying/baking foods [19]. FFQs with >15 boxes missing were excluded.
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A total of 300 μL of capillary blood was collected from earlobes or fingertips using a Microvette CB Lithium Heparin tube (SARSTEDT AG & CO., Nümbrecht, Germany) and stored at −80°C. Total haemoglobin and total A1c index were measured in a semi-automatic analyser (RANDOX SERIES HA 3839; Daytona, Crumlin, UK) according to the manufacturer’s protocol. Values were converted from Grams per decilitre to percentage using the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) equation and then to millimoles per mole to compare with World Health Organization [20] reference values. Individuals with HbA1c levels ≥42 mmol/mol (>98%) were excluded as these levels are diagnostic of prediabetes [20].

**DNA Analysis**

Participants provided a 1-mL saliva sample via a collection pot (SalivaGene Collection Module II; Stratec Molecular GmbH), which was mixed with 1 mL of DNA stabilizing solution. Participants were instructed to avoid eating, smoking or brushing their teeth for at least 1 h prior to the procedure. Genomic DNA extraction was conducted with a silica-based solid phase method PSp® SalivaGene 17 DNA Kit 1011 (Stratec Molecular GmbH) following the manufacturer’s protocol. DNA quantity and quality were evaluated in a 2 μL DNA sample by spectrophotometry (NanoDrop™ 2000/2000c; Thermo Fisher Scientific). A thermocycler (StepOnePlus; Applied Biosystems) and a predesigned TaqMan® SNP genotyping assay for rs7903146 (C____29347861_10) (Thermo Fisher Scientific) and were used to genotype samples in duplicate following the manufacturer’s protocol. Data analysis utilized Thermo Fisher Cloud Genotyping Application software. Genotyping quality rate was set above 98%.

**Statistical Analysis**

A total of 70 participants were required based on a sample calculation with an alpha error probability of 0.05, power 0.8 and large effect size ($f^2 = 0.35$) for a multiple linear regression with HbA1c as the dependent variable. Calculations were conducted using GPower 3.1.2.9 [21]. Genotype frequency distribution was tested against Hardy-Weinberg equilibrium using a χ² test using GPower 3.1.2.9 [21]. Genotype frequency distribution was compared with World Health Organization [20] reference values. Individuals with HbA1c levels ≥42 mmol/mol (>98%) were excluded as these levels are diagnostic of prediabetes [20].

### Results

#### Descriptive and Baseline Dietary Characteristics

A total of 74 subjects participated in the study. One participant from the heterozygote group with HbA1c levels of 43.9 mmol/mol was excluded as per exclusion criteria and one participant from the low-risk genotype group was excluded as an extreme outlier for HbA1c (defined as >3.0 SD from the mean value). Of the remaining 72 participants, 70 completed the FFQ and were included in the regression analysis. Genotype distribution of participants did not deviate from the Hardy-Weinberg equilibrium ($p = 0.848$). The only significant difference between the two genotype groups was HbA1c levels where T carriers (risk group) had higher levels than the CC group (32.4 ± 7.2 mmol/mol vs. 30.3 ± 7.6 mmol/mol, $p = 0.005$). Dietary intake did not differ between genotype groups (Table 1).

#### HbA1c Changes in Genotype Groups

When HbA1c levels were expressed as deviations from the overall mean, mean T carrier levels were 2.1 mmol/mol higher whereas the CC group mean was 1.9 mmol/mol.

| Characteristics       | Genotypes | p value |
|-----------------------|-----------|---------|
|                       | CC      | CT/TT   |
| Age, years            | 35 (14) | 37 (13) | 0.309  |
| Body weight, kg       | 75.7 (26.1) | 67.5 (15.3) | 0.207  |
| BMI, kg/m²             | 30.3 (7.6) | 32.4 (7.2) | 0.005  |
| Body fat, %            | 24.9 (6.0) | 23.7 (4.1) | 0.393  |
| Waist circumference, m | 28.9 (16.5) | 24.7 (10.2) | 0.301  |
| HbA1c, mmol/mol        | 35.7 (10.2) | 32.2 (10.0) | 0.207  |

Values are median (interquartile range). HbA1c, glycated haemoglobin; BMI, body mass index; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; TEI, total energy intake. p values are for differences between genotype groups (Mann-Whitney U test).
mol below. Approximately 70% (n = 22) of T carriers were above average HbA1c levels as opposed to 40% (n = 15) of CC individuals (p = 0.022; Fig. 1).

Association of Genotype and Dietary Intake with HbA1c Levels

The contribution of genotype and diet to HbA1c levels was assessed by multiple linear regression. There was no evidence of multicollinearity for any of the contributing variables (tolerance values >0.1). Studentized residuals showed normality and linearity of data. There were no outliers as assessed using leverage values and Cook’s distance. The regression model indicated that the independent variables explained 37.1% of the variance in HbA1c levels (adj. $R^2 = 0.371$, $F(16, 53) = 3.540$, $p < 0.001$). Genotype, gender, body fat, carbohydrate, protein, MUFA and SFA were the independent variables that were identified as significant contributors to HbA1c levels ($p < 0.05$). Regression coefficients, standard errors and 95% confidence intervals are illustrated in Table 2.

Discussion

This study identified that the risk allele of a common SNP in the TCF7L2 gene (rs7903146), is associated with higher HbA1c levels and therefore T2D risk in healthy adults. Elevated body fat and gender were also associated with T2D risk as were intakes of carbohydrate, protein, MUFA, and SFA.

Association between TCF7L2 rs7903146 and T2D Risk

TCF7L2 rs7903146 has been implicated as a significant genetic predisposition to T2D across different populations [18]. It has been shown that T allele carriers have higher T2D risk than homozygous individuals for the major allele [22]. Similarly, this study identified that healthy carriers of the T allele had greater HbA1c levels confirming the protective effect of the CC genotype. T2D risk was

![Figure 1: Individual HbA1c deviations from average for each genotype group. HbA1c, glycated haemoglobin.](image-url)

Table 2. Summary of multiple linear regression outcomes with HbA1c levels as the outcome variable

| Variable          | B    | SE$_B$ | $\beta$ | 95% CI          |
|-------------------|------|--------|---------|-----------------|
| Genotype          | 0.395| 0.106  | 0.382** | 0.182/0.608     |
| Age               | 0.009| 0.006  | 0.186   | $-0.002/0.021$  |
| Gender            | $-0.651$ | 0.305  | $-0.599*$| $-1.262/-0.040$ |
| Body weight       | $-0.021$ | 0.011  | $-0.633$| $-0.043/0.001$  |
| Body fat          | 0.052 | 0.017  | 1.038** | 0.018/0.085     |
| Dietary Carbohydrate | 0.080 | 0.025  | 1.068** | 0.030/0.130     |
| Dietary Protein   | 0.088 | 0.027  | 0.760** | 0.034/0.141     |
| Dietary MUFA      | 0.084 | 0.039  | 0.425*  | 0.006/0.163     |
| Dietary PUFA      | 0.086 | 0.057  | 0.314   | $-0.028/0.200$  |
| Dietary SFA       | 0.112 | 0.038  | 0.595*  | 0.036/0.188     |

*B*, unstandardized regression coefficient; HbA1c, glycated haemoglobin; SE$_B$, standard error of coefficient; $\beta$, standardized coefficient; CI, confidence interval; T2D, type 2 diabetes; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids, SFA, saturated fatty acids. *$p < 0.05$. **$p < 0.001$. 
independently elevated by body fat content \( (p < 0.005; 95\% \text{ CI} \ 0.018/0.085, B = 0.052) \) and gender, with females demonstrating lower HbA1c levels \( (p < 0.005, 95\% \text{ CI} \ -1.262/-0.040, B = -0.651) \). A previous study also observed an increased that T2D risk increases after adjusting for body composition in a healthy population in carriers of the risk allele. More specifically, T allele carriers had higher nocturnal glucose, reflecting impaired blood glucose regulation, particularly in those with greater body fat content and body weight \( (p = 0.03) \) [23]. Several studies have argued the role of TCF7L2 and its association with disruption of \( \beta \)-cell function [24, 25]. Excess body fat can increase insulin demand also impairing \( \beta \)-cell function [26]. Impairment of \( \beta \)-cells may be compounded in individuals with elevated body fat content and the rs7903146 risk allele.

**Association of Dietary Intake and T2D Risk**

Evidence from the Diabetes Prevention Study shows an association between the TCF7L2 polymorphism and T2D for TT genotypes that followed a 4-year dietary and lifestyle intervention. One of the aims of the intervention was to decrease SFA intake and the results suggest that environmental factors reduce prevalence of T2D in TT genotypes with dietary fat intake being the main contributor [27]. Likewise, Phillips et al. [13] showed further deterioration in insulin sensitivity in high SFA consumers \( (\geq 15.5\% \text{ of TEI}) \) who are also carriers of the T allele high risk.

Plasma insulin concentration was higher \( (p = 0.025) \) and insulin sensitivity was impaired in the high risk group \( (T \text{ allele carriers}) \) than the control group \( (p = 0.03) \). In the same study, MUFA consumption \( (14\% \text{ of TEI}) \) moderately reduced metabolic syndrome risk \( (OR = 2.35) \). Similar findings were reported by Corella et al. [14] who showed that adherence to a Mediterranean diet rich in oleic acid, modulates the effect of the TCF7L2 polymorphism on fasting glucose concentrations in TT carriers \( (p = 0.001) \). The present study confirms the association between SFA and HbA1c. Conversely, MUFA intake was positively associated with HbA1c. This contradictory finding may indicate a higher optimal level at which MUFA intake is beneficial to carriers of the risk allele \( (14.8\% \text{ TEI in the current study against 19.5\% TEI in the study by Corella et al. [14]}) \). However, the present study did not control dietary intakes resulting in a wider range of dietary constituents; therefore, further investigation is warranted to confirm this hypothesis.

The associations between protein and total carbohydrate intakes with HbA1c reported in this study are novel. The present study observed that both macronutrients are positively associated with HbA1c; however, it is not clear if protein and carbohydrate intake alter the effect of TCF7L2 polymorphism on T2D risk. Two other studies have investigated these associations without showing evidence of an interaction [14, 28]. Corella et al. [14] investigated in a randomized trial the effects of the Mediterranean diet for the different variants of rs7903146. They observed a highly significant association \( (p < 0.001) \) between the TCF7L2 polymorphism and fasting glucose but no effects of protein or carbohydrate intake and glycaemic indices. However, their study population comprised individuals with a high cardiovascular and T2D risk, which is a notably different group compared to the present study. Hindy et al. [28] who conducted a cohort study, reported that dietary fibre intake may modify the association between TCF7L2 rs7903146 and that higher fibre intake may be associated with protection from T2D only among non-risk allele carriers. They did not report any associations for other macronutrients, but they did not correct for collinearity among the dietary variables. Macronutrient intakes are likely to be collinear considering that diets include a mixture of macronutrients and this lack of correction is likely to have caused discrepancies with our study where collinearity was addressed. Several studies suggest that some consumers of high carbohydrate and animal protein are more likely to present impaired glucose and insulin response [29, 30] potentially due to higher intake of dietary components linked to T2D risk such as sugar and red meat but more research is needed to identify whether genetic susceptibility is a co-factor.

This study identified that carriers of the T allele of rs7903146 are susceptible to T2D with carbohydrate, protein, SFA, and MUFA intake as independent risk factors along with gender and body fat content. Regression modelling suggests dietary factors such as carbohydrate, have a stronger association with HbA1c levels than genotype \( (\beta = 1.068 \text{ and } \beta = 0.382, \text{ respectively}) \). Diet is a modifiable factor and genetics effects modulated by dietary intake may have a potential impact on public health [13]. However, genetic-diet interactions were not considered in the current study as the aim was on identifying key risk factors. Gene-diet interactions should ideally be investigated through intervention studies with larger sample sizes [31].

**Strengths and Limitations**

The study was powered to detect associations of genetics and diet with T2D. The use of HbA1c reflects long-term blood homeostasis reducing misclassification of T2D status, therefore improving accuracy [32]. The inclusion of

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healthy individuals increases the applicability of the findings for screening purposes. This may reduce health-care costs and other health issues associated with T2D. The addition of several dietary components provides a more complete model of individual risk factors. However, FFQs rely on memory and willingness of the respondents to disclose details and risk misclassification. Ideally, dietary intake should be evaluated through a combination of validated FFQ plus a minimum of three dietary records to improve accuracy [33]. Also, the study would benefit from including instantaneous measures of blood glucose as well, such as fasting plasma glucose. This would facilitate better comparison with existing literature and a direct comparison of appropriateness between the two measures.

**Conclusions**

This study replicated prior results reporting genetic effects of TCF7L2 rs7903146 polymorphism on T2D in healthy individual carriers of risk-allele utilizing a more appropriate outcome measure than previous studies. Dietary intakes of carbohydrate, protein, SFA, and MUFA, appear to be associated with HbA1c levels to a greater extent than genotype. However, further investigation regarding the molecular mechanism in any potential gene-diet interaction is warranted. Future research should consider all variables, including genetic predisposition with other variants of TCF7L2, ethnicity, and long-term nutritional interventions to develop strategies for the prevention of T2D.

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**Statement of Ethics**

The study was carried out under the supervision and with the approval from the Ethics Committee from St Mary’s University (approval: SMEC_2018-19_034), which covers written informed consent from all participants. This research was conducted in line with the Declaration of Helsinki.

**Conflict of Interest Statement**

I.C.R.P. and Y.M. are associated with the wellbeing company Nell Health and L.P. with the wellbeing company DNAFuel LTD.

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**Author Contributions**

I.C.R.P., S.S., and Y.M. designed the experiment. I.C.R.P. and S.S. conducted the recruitment, data collection, and data analysis. I.C.R.P., L.P., C.A.-M.G, and A.K. conducted the present manuscript. Supervision of the project was conducted by Y.M. All authors discussed the findings and associations at all stages.

**Data Availability Statement**

All data generated or analysed during this study are included in this article. Further enquires can be directed to the corresponding author.

**References**

1. Asma S, Lozano R, Chatterji S, Swaminathan S, de Fátima Marinho M, Yamamoto N, et al. Monitoring the health-related Sustainable Development Goals: lessons learned and recommendations for improved measurement. *Lancet*. 2020;395(10219):240–6.
2. IDF. International Diabetes Federation (IDF) diabetes atlas. 9th ed. IDF; 2019. Report No.
3. Cersosimo E, Triplitt C, Solis-Herrera C, Mandarino LJ, DeFronzo RA. Pathogenesis of type 2 diabetes mellitus. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, Dungan K, Grossman A, et al., editors. Endotext [Internet]. South Dartmouth, MA: MDText.com, Inc.; 2000 [cited 2020 Jun 10]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK279115/.
4. Bellou V, Belbasis L, Tzoulaki I, Evangelou E. Risk factors for type 2 diabetes mellitus: an exposure-wide umbrella review of meta-analyses. *PLoS One*. 2018 Mar 20 [cited 2020 Jun 10];13(3):e0194127.
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5 Neuenschwander M, Ballon A, Weber KS, Norat T, Aune D, Schwingshackl L, et al. Role of diet in type 2 diabetes incidence: umbrella review of meta-analyses of prospective observational studies. BMJ. 2019 Jul 3; [cited 2020 May 18];366:l2368.

6 Schwingshackl L, Hoffmann G, Lampousi A-M, Knüppel S, Iqbal K, Schwedhelm C, et al. Food groups and risk of type 2 diabetes mellitus: a systematic review and meta-analysis of prospective studies. Eur J Epidemiol. 2017 [cited 2020 May 18];32(5):363–75.

7 Xue A, Wu Y, Zhu Z, Zhang F, Kemper KE, Schwingshackl L, Hoffmann G, Lampousi A-M, Ballon A, Weber KS, et al. Genome-wide association analyses identify 143 risk variants and putative regulatory mechanisms for type 2 diabetes. Nat Commun. 2018;9(1):2941.

8 Tong Y, Lin Y, Zhang Y, Yang J, Zhang Y, Liu H, et al. Association between TCF7L2 gene polymorphisms and susceptibility to type 2 diabetes mellitus: a large Human Genome Epidemiology (HuGE) review and meta-analysis. BMC Med Genet. 2009 Feb 19;10:15.

9 Zeggini E, Scott LJ, Saxena R, Voight BF, Marchini JL, Hu T, et al. A global referen-cial questionnaire data into nutrient and food group analysis of prospective studies. Eur J Epidemiology. 2012 May;34(Suppl 2):S184–90.

10 Zeggini E, Scott LJ, Saxena R, Voight BF, Marchini JL, Hu T, et al. Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. Nat Genet. 2008 Aug;40(5):638–45.

11 Daniele G, Gaggini M, Comassi M, Bianchi C, Basta G, Dardano A, et al. Glucose metabolism kinase-3beta. J Biol Chem. 2005 Jan 14;280(2):1457–64.

12 Yi F, Brubaker PL, Jin T. TCF-4 mediates cell type-specific regulation of proglucagon gene expression by beta-catenin and glycogen synthase kinase-betaA. J Biol Chem. 2005 Jan 14;280(2):1457–64.

13 Phillips CM, Goumidi L, Bertrais S, Field MR, McMannus R, Herbreg S, et al. Dietary saturated fat, gender and genetic variation at the TCF7L2 locus predict the development of metabolic syndrome. J Nutr Biochem. 2012 Mar;23(3):239–44.

14 Corella D, Carrasco P, Sorli JV, Estruch R, Rico-Sanz J, Martinez-González MA, et al. Mediterranean diet reduces the adverse effect of the TCF7L2-rs7903146 polymorphism on cardiovascular risk factors and stroke incidence: a randomized controlled trial in a high-cardiovascular-risk population. Diabetes Care. 2013 Nov;36(11):3830–11.

15 Le Bacquer O, Kerr-Conte J, Gargani S, Delalleau N, Huyvaert M, Gmyr V, et al. TCF7L2 rs7903146 impairs islet function and morphology in non-diabetic individuals. Diabetologia. 2012 Oct;55(10):2677–81.

16 Mitchell RK, Mondragon A, Chen L, Mcginty JA, French PM, Ferrer J, et al. Selective disruption of Tcf7l2 in the pancreatic β cell impairs secretory function and lowers β cell mass. Hum Mol Genet. 2015 Mar 1;24(5):1390–9.

17 Bonora E, Tuomilehto J, The pros and cons of diagnosing diabetes with A1C. Diabetes Care. 2011 May;34(Suppl 2):S184–90.

18 Franklin CS, Aulchenko YS, Huffman JE, Vi- tart V, Hayward C, Polasek O, et al. The TCF7L2 diabetes risk variant is associated with Hba(1C) levels: a genome-wide association meta-analysis. Ann Hum Genet. 2010 Nov;74(6):471–8.

19 Mulligan AA, Rubin RN, Bhaniani A, Parry- Smith DJ, O’Connor L, Khawaja AP, et al. A new tool for converting food frequency questionnaire data into nutrient and food group values: FETA research methods and availability. BMJ Open. 2014 Mar;4(3):e004503.

20 World Health Organisation. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. 2011 Sep [cited 2020 Jun 12]: 299–309. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0168822711001318.

21 Faul F, Erdfelder E, Lang A-G, Buchner AG. Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007 May;39(2):175–91.

22 Cauchi S, El Achhab Y, Choquet H, Dina C, Krempler F, Weitgasser R, et al. TCF7L2 is reproducibly associated with type 2 diabetes in various ethnic groups: a global meta-analysis. J Mol Med. 2007 Jul;85(7):777–82.

23 Shim JS, Oh K, Kim HC. Dietary assessment methods in epidemiologic studies. Epidemiol Health. 2014;36:e2014009.

24 Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Sato M, et al. Influence of fat and carbohydrate proportions on the metabolic profile in patients with type 2 diabetes: a meta-analysis. Diabetes Care. 2009 May;32(5):959–65.

25 Tian S, Xu Q, Jiang R, Han T, Sun C, Na L. Dietary protein consumption and the risk of type 2 diabetes: a systematic review and Meta-Analysis of Cohort Studies. Nutrients. 2017 Sep 6;9(9):982.

26 Grimaldi KA, van Ommen B, Ordovas JM, Parnell LD, Mathers JC, Bendik I, et al. Proposed guidelines to evaluate scientific validity and evidence for genotype-based dietary advice. Genes Nutr. 2017 Dec 15 [cited 2020 Oct 2];12:35.

27 Sacks DB. AIC versus glucose testing: a comparison. Diabetes Care. 2011 Feb;34(2):518–23.

28 Wang J, Kuusisto J, Vänttinen M, Kuulasmaa T, Lindström J, Tuomilehto J, et al. Variants of transcription factor 7-like 2 (TCF7L2) gene predict conversion to type 2 diabetes in the Finnish Diabetes Prevention Study and are associated with impaired glucose regulation and impaired insulin secretion. Diabetologia. 2007 Jun;50(6):1192–200.

29 Hindy G, Sonesstedt E, Ericson U, Jing XJ, Zhou Y, Hansson O, et al. Role of TCF7L2 risk variant and dietary fibre intake on incident type 2 diabetes. Diabetologia. 2012 Oct;55(10):2646–54.

30 Tian S, Xu Q, Jiang R, Han T, Sun C, Na L. Dietary protein consumption and the risk of type 2 diabetes: a systematic review and Meta-Analysis of Cohort Studies. Nutrients. 2017 Sep 6;9(9):982.