Associations between fruit intake and risk of diabetes in the AusDiab cohort

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Conflicts of Interest:

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ABSTRACT

Background: Fruit, but not fruit juice, intake is inversely associated with type 2 diabetes mellitus (T2DM). However, questions remain about the mechanisms by which fruits may confer protection. Aims were to examine associations between intake of fruit types and 1) measures of glucose tolerance and insulin sensitivity and 2) diabetes at follow-up.

Methods: Among participants of the Australian Diabetes, Obesity and Lifestyle Study, fruit and fruit juice intake was assessed by food frequency questionnaire at baseline. Associations between fruit and fruit juice intake and 1) fasting plasma glucose, 2-h post-load plasma glucose, HOMA2 of β-cell function (HOMA2-%β), HOMA2 of insulin sensitivity (HOMA2-%S), and fasting insulin levels at baseline and 2) the presence of diabetes at follow-up (5 and 12 years) were assessed using restricted cubic splines in logistic and linear regression models.

Results: This population of 7,675 Australians (45% males) had a mean±SD age of 54±12 years at baseline. Total fruit intakes were inversely associated with serum insulin and HOMA2-%β, and positively associated with HOMA2-%S at baseline. Compared to participants with the lowest intakes (quartile 1), participants with moderate total fruit intakes (quartile 3) had a 36% lower odds of having diabetes at 5 years [OR (95% CI): 0.64 (0.44, 0.92)], after adjusting for dietary and lifestyle confounders. Associations with 12-year outcomes were not statistically significant.

Conclusion: A healthy diet including whole fruits, but not fruit juice, may play a role in mitigating T2DM risk.

Keywords: Fasting plasma glucose; 2-h post-load plasma glucose; HOMA2 of β-cell function (HOMA2-%β); HOMA2 of insulin sensitivity (HOMA2-%S); fasting insulin levels

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is characterized by impaired insulin secretion (β-cell dysfunction) and increased insulin resistance (or resistance to insulin mediated glucose uptake). It accounts for more than two million deaths annually (1) and is the seventh leading cause of disability worldwide (2). An estimated 451 million people worldwide have diabetes, with numbers postulated to exceed 693 million in 2045 (3). Given its global prevalence, there is an urgent need for evidence-based strategies targeting T2DM prevention.

Overwhelming evidence supports the promotion of a healthy diet and regular physical activity for mitigating the risk of T2DM (4). In particular, an inverse association between fruit intake and T2DM incidence has been reported in a pooled analysis of three large observational studies (5). Further, adherence to Australian Dietary Guidelines recommendations for fruit consumption (2 serves [150 g] per day for adults) was associated with a 32% lower risk of T2DM over 12 years in the Australian Diabetes, Obesity and Lifestyle Study (6). The authors report that adherence to these recommendations could have prevented 23% of T2DM cases (population attributable fraction: 23.3 [7.3–38.2]). However, it is likely that not all fruits offer equal protection against diabetes as heterogeneity in the associations between individual fruit consumption and risk of T2DM has been reported (5). Specifically, in three prospective cohorts of American men and women, a higher consumption of blueberries, grapes, apples, bananas, and grapefruit were individually associated with a significantly lower risk of T2DM (5). Interestingly, variances in glycemic index and glycemic load did not explain the differential association of specific fruits with risk of T2DM.

Insulin resistance and β-cell dysfunction play a critical role in the development of T2DM (7), however, relationships between fruit intake and measures of insulin resistance and β-cell

dysfunction are not yet understood. The investigation of such relationships may provide valuable insight into the mechanisms by which a higher fruit intake may lower the risk of T2DM. Therefore, the aims of this study were to examine associations between intakes of total fruit, individual fruits commonly consumed by the study cohort, and fruit juice and (i) measures of insulin resistance and β-cell dysfunction and (ii) incident diabetes at 5 and 12 years follow-up, in a cohort of Australian men and women.

METHODS:

Study Population

Participants included in this study were men and women aged ≥25 years, recruited to the Australian Diabetes, Obesity and Lifestyle Study (AusDiab) between 1999 and 2000. The methods and response rates of the AusDiab cohort have been described previously (8). In brief, AusDiab is a national population-based survey of diabetes mellitus prevalence and associated risk factors in Australian adults, recruited from the seven states and territories of Australia in 1999–2000 (n=11,247), with follow up in 2004/05 (n=6,400) and 2011/2012 (n=4,614). From the 11,247 participants who attended the biomedical examination at baseline, we excluded participants who did not complete a food frequency questionnaire (FFQ) at baseline (n=204), had improbable energy intakes (<2,500 kJ/day or >14,500 kJ/day for females and <3,300 kJ/day or >17,500 kJ/day for males (9, 10); n=342), were pregnant (n=45), had diabetes at baseline (n=968), had missing data for important covariates (n=642), and who had missing outcome data at baseline (n=1,371). This left 7,675 participants remaining for analyses at baseline. Of these, follow-up data was available for 4,674 participants at 5 years and 3,518 participants at 12 years (**Figure 1**).

The study was approved by The Human Research Ethics Committees of the International Diabetes Institute, and the Alfred Hospital (Melbourne, Australia).

Exposures

The exposures of interest for this study were intakes of total fruit, individual fruits commonly consumed by cohort participants, and fruit juice. Habitual dietary intake of participants at baseline was assessed using a semi-quantitative FFQ developed by the Cancer Council of Victoria (11-13). Participants were asked to indicate their usual frequency of intake of food items, over the previous 12 months, using a list of 74 food items with 10 frequency response options ranging from "never" to "three or more times per day". Food items included fruit juice (unspecific) and 10 different types of fruit [**Supplementary Figure 1 (14)]**. Additional questions regarding frequency of intake were used to adjust these results, which often over-estimate intakes. Portion size was calculated using photographs of scaled portions of different food types. Nutrient intake calculations were analyzed by Cancer Council Victoria using the NUTTAB95 food nutrient database and were supplemented by other data where necessary. To reduce the chance of a Type 1 error, only fruits whose intake contributed >10% to total fruit intake were investigated discretely.

Study outcomes

Primary outcomes included measures of fasting plasma glucose (FPG), 2-h post-load plasma glucose (PLG), HOMA2 of β-cell function (HOMA2-%β), HOMA2 of insulin sensitivity (HOMA2-%S), and fasting insulin levels obtained at baseline. FPG and PLG were determined using a spectrophotometric-hexokinase method and serum insulin was measured using an automated chemiluminescence immunoassay. The HOMA2 computer model was used to estimate insulin sensitivity (HOMA2-%S) and β-cell function (HOMA2-%B) from fasting insulin and glucose concentrations; this method has been used extensively in

epidemiological studies (15). The secondary outcome was incident T2DM at follow-up (5 and 12 years). T2DM was classified as fasting plasma glucose ≥7.0 mmol/L, 2-h post-load plasma glucose ≥11.1 mmol/L, or current treatment with insulin or oral hypoglycemic agents (16).

Covariates

Baseline demographic data, including age, sex (male/female), education level (never to some high school/completed University or equivalent), physical activity (sedentary = 0 min/week; insufficient <150 min/week minutes; and sufficient ≥ 150min/week), smoking status (current/former/never), income, and parental history of diabetes (yes/no) were collected using interviewer-administered questionnaires, as described previously (17). The Socio-Economic Indexes for Areas (SEIFA) as reported by the Australian Bureau of Statistics (18) was obtained. To calculate BMI, height was measured to the nearest 0.5 cm without shoes using a stadiometer and weight was measured without shoes and excess clothing to the nearest 0.1 kg using a mechanical beam balance (8, 19). Self-reported history of cardiovascular disease (yes/no) was assessed as described previously (20). Data on intake of dietary covariates were obtained from the FFQ described above.

Statistical Analysis

Statistical analyses were undertaken using STATA/IC 15.1 (StataCorp LLC) and R statistics (R Core Team, 2019 (21)). As the primary outcomes of interest were non-negative and positively skewed, generalised linear models with a Gamma distribution and log-link were used to examine associations with all exposures (continuous). To investigate potential non-linearity of the relationships, exposures were modelled using restricted cubic splines. P-values for the overall effect of the exposure on the response (false discovery rate corrected)

and for a test of non-linearity were obtained using likelihood ratio tests to compare appropriate nested models. Associations are presented graphically using the 'effects' R package (22). To determine where significant differences between quartiles of intake exist, ratios of means and 95% CIs were obtained from the model with the exposure fitted as a continuous variable through a restricted cubic spline and are reported for the median intake in each quartile (Q) relative to the median intake in Q1. Logistic regression models were used to investigate the relationship between baseline fruit intake and the secondary outcome of incident diabetes at 5 and 12 years. All odds ratios (ORs) and 95% CIs were obtained from the model with the exposure fitted as a continuous variable through a restricted cubic spline using the 'rms' R package (23); OR estimates are graphed over a fine grid of x values with the median intake in Q1 as the reference point and are also reported for the median of each quartile. For all regression models, three models of adjustment were used: Model 1 adjusted for age (years) and sex (male/female); Model 2 adjusted for age, sex, physical activity levels (sedentary, insufficient, sufficient), level of education (never to some high school, completed university or equivalent), SEIFA (socio-economical index for areas categorised intro quintiles), income, BMI (kg/m^2), smoking status (current smoker, ex-smoker, non-smoker), self-reported prevalence of cardiovascular disease (yes/no), and parental history of diabetes (yes/no); Model 3 adjusted for all covariates in Model 2 plus energy intake, and intakes (g/day) of alcohol, vegetables, red meat and processed meat. For visual simplicity, in all graphs presented, the x-axis was truncated at 3 standard deviations (SD) above the mean.

RESULTS

This population of 7,674 Australians (45% males), had a mean ± SD age of 54 ± 12 years at baseline and the median [IQR] total fruit intake was 162 [95 – 283] g/day. Relative to participants with the lowest total fruit intakes (Q1), those with the highest intakes (Q4) were

more likely to be female, slightly older, more physically active, less disadvantaged, and have a higher degree of education and were less likely to be current smokers (**Table 1**). Although participants in Q4 had a higher total energy intake than participants in Q1, their underlying dietary pattern tended to be slightly heathier in that they ate more vegetables and less red and processed meat (**Table 1**). Participants with no follow-up data after baseline had, on average, a slightly lower intake of fruit and vegetables, were slightly less physically active, less likely to have a higher degree of education and were more likely to smoke [**Supplementary Table 1 (14)**].

The most commonly consumed fruit was apples, contributing approximately 23% to total fruit intake, followed by bananas (~20%), and oranges and other citrus fruits [~18%; **Supplementary Figure 1 (14)**]. All other fruits contributed less than 8% each to total fruit intake and were therefore not assessed discretely in subsequent analyses.

Cross-sectional associations between fruit intake and measures of fasting glucose, glucose tolerance and insulin sensitivity at baseline

Total fruit intake was significantly inversely associated with serum insulin and HOMA2-%β, and significantly positively associated with HOMA2-%S (false discovery rate corrected $p \leq 0.05$ for all; **Figure 2**). Total fruit intake was not associated with PLG or FPG [**Figure 2** and **Supplementary Figure 2 (14)**]. Compared to participants in the lowest total fruit intake quartile, participants in the highest intake quartile had a 3% lower PLG [0.97 (0.96, 0.99)], a 5% lower serum insulin [0.95 (0.93, 0.98)] a 2% lower HOMA2-%β [0.98 (0.96, 1.00)], and a 6% higher HOMA2-%S [1.06 (1.03, 1.09)], after multivariable adjustments (Model 2; **Tables 2 and 3**). Adjusting for potential dietary confounders (Model 3) did not change the associations.

Of the individual fruit types, apple intakes were significantly inversely associated with serum insulin (p=0.035) and non-linearly inversely associated with PLG [p<0.001; $p_{non\text{-}linearity}$<0.001; **Supplementary Figure 3 (14)]**. Although apple intakes appeared to be inversely associated with HOMA2-%B and positively associated with HOMA2-%S, these associations did not reach statistical significance after adjustments were made for dietary confounders. Intakes of orange and other citrus fruits, bananas and fruit juice were not significantly association with any outcome [**Tables 2 and 3; Supplementary Figures 4- 6 (14)**].

Prospective associations between fruit intake and incident diabetes at 5 years and 12 years.

Of the 4,674 participants with follow-up at 5 years, 179 participants had diabetes. Total fruit intake appeared to be non-linearly inversely associated with incident diabetes at 5 years follow-up (**Figure 3**). Compared to participants with the lowest intakes (Q1), participants with moderate total fruit intakes (Q3) had a 36% lower odds of having diabetes at 5 years [OR (95% CI): 0.64 (0.44, 0.92)], after multivariable adjustments [Model 3; **Supplementary Table 2 (14)**]. Apparent inverse associations did not reach statistical significance for intakes of individual types of fruit after adjusting for potential dietary and lifestyle confounders (**Figure 3 and Supplementary Table 2(14)**]. Of the 3,518 participants with follow-up at 12 years, 247 participants had diabetes. Odds ratios indicate a lower odds of diabetes for moderate to high intakes of total fruit, apples, orange and other citrus fruits, and bananas although confidence intervals were wide and associations were not statistically significant in Model 3 [**Supplementary Table 3 (14)**].

DISCUSSION

In this cohort of 7,675 Australian men and women, higher total fruit intakes were associated with better measures of glucose tolerance and insulin sensitivity. Furthermore, a moderate to high total fruit intake was associated with a lower odds of diabetes after 5 years of follow-up.

Insulin resistance, in concert with β-cell dysfunction and obesity, is a key driver of the pathophysiology of T2DM (7). HOMA2 is one approach of assessing β-cell function and insulin resistance (or insulin sensitivity) by means of fasting glucose and insulin values (15). In the present study, higher total fruit intakes were associated with higher insulin sensitivity and lower β-cell function in a dose-response manner. At a glance, the inverse association between fruit intake and β-cell function may seem counter-intuitive. However, the HOMA2 of β-cell function measurement actually reflects insulin secretion (or β-cell 'activity') rather than β-cell 'function' (24); in this context, the lower values likely reflect higher insulin sensitivity (15). Although statistically significant, the higher in β-cell activity and insulin sensitivity seen with higher intakes of fruit translated to a small decrease in PLG which could be considered clinically minor. While this study sheds light on the physiological impact of fruit, further research is warranted.

In a recent meta-analysis of 15 observational cohort studies, with 70,968 cases of T2DM, a borderline inverse association was observed between total fruit intake and odds of having T2DM (RR: 0.96; 95% CI 0.93–1.00 for high versus low fruit intake) (4). As observed in the present study, there was evidence that this inverse relationship was non-linear, plateauing at fruit intakes of approximately 200 – 300 g/day (4). While associations for individual fruits were not examined in this meta-analysis, the largest of the included cohort studies (pooling data from three prospective cohorts of US men and women) reported that associations with T2DM risk differed significantly among intakes of individual fruits. Specifically, the risk of

T2DM for intakes of three servings/week was 26% lower for blueberries, 12% lower for grapes and raisins, 7% lower for apples and pears, 5% lower for bananas, 5% lower for grapefruit, and 10% higher for cantaloupe (5). In the present study, evidence of an inverse association between higher intakes and incident diabetes at 5 years was apparent for apples, bananas, and orange and other citrus fruits. That associations did not reach statistical significance after multivariable adjustments may be due to a low statistical power owing to the relatively low number of events. Associations were not statistically significant for 12-year outcomes, perhaps due the longer time lag between exposure assessment and outcome.

The biological mechanisms underpinning the beneficial effects of fruits on glucose regulation and diabetes risk are likely multifaceted. Besides their low contribution to energy intake, most fruits typically have a low glycemic load, whilst being rich in fibre, vitamins, minerals, and phytochemicals, all of which may play a contributory role (25). Potential mechanistic evidence is mainly for fibre (26); both insoluble and soluble fiber are reported to improve glycemic control. However, recent evidence suggests that more benefits may be gained from fermentation of soluble fibres by the gut microbiome, increasing production of short-chain fatty acids (SCFAs) which have been shown to modulate glucose metabolism (27, 28). Furthermore, many fruits, including apples, are rich in flavonoids, a class of phytochemicals which are reported to improve insulin sensitivity, potentially by decreasing apoptosis and promoting proliferation of pancreatic β-cells, and reduce muscular inflammation and oxidative stress (29, 30). Moreover, fruit intake may indirectly influence T2DM risk by preventing or managing excess adiposity, possibly via higher dietary fibre contributing towards satiety (31). Interestingly, although there was evidence that higher banana intakes may be associated with a lower risk of diabetes at 5 years, banana intakes were not significantly associated with measures of glucose tolerance and insulin sensitivity at baseline. This finding warrants investigation in other cohorts.

A positive association between fruit juice consumption and T2DM has been reported previously (5, 32, 33). In a meta-analysis of 12 prospective cohort studies, a one serving/day higher intake of fruit juice was associated with a 10% higher risk of T2DM (RR (95% CI): 1.10 (1.01, 1.20), after adjusting for adiposity and within-person variation (33). For this reason, in the present study, fruit juice intake was not included in the calculation of total fruit intake. In the present study, we report no association between fruit juice consumption and measures of insulin resistance and β-cell dysfunction or incident diabetes. That an association was observed between intakes of whole fruit, but not fruit juice, may be due to the relatively high glycemic load of fruit juices and reduced levels of beneficial fibres in comparison to whole fruit (34). This may lead to larger and more rapid increases in serum glucose and insulin levels (35). Data also suggest that fruit juice, including fruit juice with added fibre, does not trigger satiety to the extent that whole fruit does (36). Our findings support that of a meta-analysis of 18 randomised controlled trials which reported that, compared with the control group, 100% fruit juice had no significant effect on fasting blood glucose, fasting blood insulin, or HbA1c (37). However, the interventions in the aforementioned trials (predominantly grape juice, pomegranate juice, and grapefruit juice) are not fruit juices typically consumed and were often sugar-free, limiting generalisation.

The strengths and limitations of the study should be acknowledged to facilitate appropriate interpretation of the findings. Limitations, characteristic of observational studies, apply in that we are not able to infer causality or rule out residual confounding. Due to the relative low intakes of certain fruits, particular those that are not available all year around, we did not investigate associations for intakes of all fruits captured in the FFQ. We also acknowledge that participants of the AusDiab study were likely of a higher socio-economic status than those who did not respond to the original survey (20) and that participants with follow-up

data tended to be healthier than those lost to follow-up; associations warrant investigation in other populations.

In conclusion, findings from this study support encouragement of the consumption of whole fruits, but not fruit juice, to preserve insulin sensitivity and mitigate T2DM risk. Promoting a healthy diet and lifestyle which includes the consumption of popular fruits such as apples, bananas and oranges, with widespread geographical availability, may lower T2DM incidence.

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Authors' Contributions:

NPB designed research (project conception, development of overall research plan, and study oversight); DJM, RMD, and JES conducted the original cohort study; NPB analysed the data; NPB wrote the manuscript and had primary responsibility for final content; all authors assisted with interpretation of the results and critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

Data Availability Statement: Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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Figure Legends:

Figure 1. Consort flow diagram. FFQ, food frequency questionnaire.

Figure 2. Graphical representation of the multivariable-adjusted dose-response relationship between total fruit intake and baseline (a) fasting serum insulin, (b) HOMA2 of β-cell function (c) HOMA2 of insulin sensitivity, and (d) 2-h post-load plasma glucose, obtained by generalized regression models with the exposure included as a restricted cubic spline (n=7,675). The HOMA2 computer model was used to estimate HOMA of insulin sensitivity HOMA of β-cell function. Blue shading represents 95% confidence intervals. The rug plot along the bottom of each graph depicts each observation. All analyses were adjusted for age, sex, physical activity levels, level of education, SEIFA (socio-economical index for areas), income, BMI, smoking status, prevalence of cardiovascular disease, parental history of diabetes, and intakes of vegetables, alcohol, red meat, processed meat and energy. P-values for the effect of the exposure on the response (false discovery rate corrected) were obtained using likelihood ratio tests.

Figure 3. Multivariable-adjusted associations between intakes of total fruit, individual fruit types, and fruit juice and presence of diabetes (fasting plasma glucose ≥7.0 mmol/L, 2-h post-load plasma glucose ≥11.1 mmol/L, or current treatment with insulin or oral hypoglycemic agents) at 5 years (n=4,674). Values are odds ratios and 95% CI and are comparing the specific level of fruit intake (horizontal axis) to the median intake for participants in the lowest intake quartile. All analyses were adjusted for age, sex, physical activity levels, level of education, SEIFA (socio-economical index for areas), income, BMI, smoking status, prevalence of cardiovascular disease, parental history of diabetes, and intakes of vegetables, alcohol, red meat, processed meat and energy (Model 3).

Table 1. Baseline characteristics of the study population

	Whole population (n=7,675)	Total fruit intake quartiles			
		Q1 (n=1,920)	Q2 (n=1,920)	Q3 (n=1,918)	Q4 (n=1,917)
Total fruit intake (g/day), median [IQR]	162 [95 – 283]	62 [53 – 75]	122 [109 – 137]	230 [203 – 253]	372 [325 – 448]
Demographics					
Age (years)	54 ± 12	51 ± 11	53 ± 12	55 ± 13	55 ± 12
Sex (male), n (%)	3,439 (44.8)	989 (51.5)	909 (47.3)	676 (35.2)	865 (45.1)
BMI (kg/m^2)	26.8 ± 4.7	27.0 ± 4.8	26.8 ± 4.5	26.6 ± 4.7	26.9 ± 4.7
SEIFA score, median [IQR]	1,033 [972 – 1,079]	1,008 [966 – 1,075]	1,032 [972 – 1,075]	1,044 [976 – 1,080]	1,048 [974 – 1,086]
Physical activity, n (%)					
Sedentary	1,308 (17.0)	470 (24.5)	316 (16.5)	274 (14.3)	348 (18.2)
Insufficient	2,377 (31.0)	617 (32.1)	634 (33.0)	599 (31.2)	527 (27.5)
Sufficient	3,990 (52.0)	833 (43.4)	970 (50.5)	1,045 (54.5)	1,142 (59.6)
Smoking status, n (%)					
Current	1,097 (14.3)	493 (25.7)	271 (14.1)	187 (9.7)	146 (7.6)
Former	2,319 (30.2)	552 (28.8)	582 (30.3)	597 (31.1)	588 (30.7)
Never	4,259 (55.5)	875 (45.6)	1,067 (55.6)	1,134 (59.1)	1,183 (61.7)
Education, n (%)					
Never, primary or high school	3,114 (40.6)	845 (44.0)	775 (40.4)	778 (40.6)	716 (37.4)
Secondary education	4,561 (59.4)	1,075 (56.0)	1,145 (59.6)	1,140 (5.9)	1,201 (62.6)
Prevalent CVD, n (%)	609 (7.9)	128 (6.7)	145 (7.8)	176 (9.2)	160 (8.3)
Family history of diabetes, n (%)	1,366 (17.8)	351 (18.3)	367 (19.1)	308 (16.1)	340 (17.7)
Dietary characteristics, *median [IQR]*					
Total energy intake (kj)	7,803 ± 2,660	7,534 ± 2,728	7,668 ± 2,491	7,454 ± 2,483	8,557 ± 2,776
Alcohol intake (g/d)	6 [1 – 19]	7 [1 – 23]	6 [1 – 20]	5 [1 – 15]	5 [0 – 17]
Sugar intake (g/d)	87 [67 – 112]	71 [53 – 97]	81 [63 – 105]	87 [70 – 108]	107 [88 – 134]
Vegetable intake (g/d)	162 [118 – 218]	152 [103 – 208]	156 [117 – 210]	158 [116 – 206]	187 [140 – 247]
Red meat (g/d)	59 [34 – 96]	67 [38 – 111]	61 [37 – 94]	53 [30 – 83]	59 [33 – 98.7]
Processed meat (g/d)	17 [8 – 31]	21 [10 – 35]	19 [9 – 32]	14 [7 – 27]	14 [6 – 30]

Results are presented as means ± unless otherwise stated.
CVD, cardiovascular disease; SEIFA, Socio-Economic Indexes for Areas

Table 2. Associations between fruit intake and post load plasma glucose (n=7,675).

	Fruit intake quartiles			
	Q1	Q2	Q3	Q4
Total fruit	62 g/day (0 – 95)	122 g/day (95 – 162)	230 g/day (162 – 283)	372 g/day (283 – 961)
PLG (mmol/L)	5.8 (4.9 – 6.9)	5.8 (4.9 – 7.0)	5.9 (5.0 – 7.0)	5.8 (4.9 – 6.9)
No. participants	1,920	1,920	1,918	1,917
Model 1	ref.	1.00 (0.99, 1.01)	0.98 (0.97, 1.00)	0.97 (0.96, 0.99)
Model 2	ref.	1.00 (0.98, 1.01)	0.98 (0.97, 1.00)	0.97 (0.96, 0.99)
Model 3	ref.	1.00 (0.99, 1.01)	0.99 (0.97, 1.00)	0.98 (0.97, 1.00)
Apple	4 g/day (0 – 10)	18 g/day (10 – 30)	46 g/day (30 – 69)	113 g/day (69 – 706)
PLG (mmol/L)	5.9 (5.0 – 7.2)	5.8(4.8 – 6.9)	5.8 (4.9 – 7.0)	5.7 (4.8 – 6.8)
No. participants	1,928	1,914	1,915	1,918
Model 1	ref.	0.98 (0.96, 0.99)	0.97 (0.96, 0.98)	0.96 (0.95, 0.98)
Model 2	ref.	0.97 (0.96, 0.98)	0.96 (0.95, 0.98)	0.96 (0.95, 0.98)
Model 3	ref.	0.97 (0.96, 0.98)	0.97 (0.96, 0.98)	0.97 (0.95, 0.98)
Oranges and other citrus	2 g/day (0 – 6)	12 g/day (6 – 19)	33 g/day (20 – 57)	96 g/day (57 – 479)
PLG (mmol/L)	5.9 (5.0 – 7.2)	5.7 (4.8 – 6.7)	5.8 (4.9 – 7.0)	5.9 (5.0 – 7.0)
No. participants	1,919	1,922	1,919	1,915
Model 1	ref.	0.99 (0.98, 1.01)	0.99 (0.97, 1.00)	0.98 (0.97, 1.00)
Model 2	ref.	0.99 (0.98, 1.00)	0.99 (0.97, 1.00)	0.99 (0.97, 1.00)
Model 3	ref.	0.99 (0.98, 1.00)	0.99 (0.98, 1.00)	0.99 (0.98, 1.01)
Bananas	4 g/day (0 – 10)	16 g/day (10 – 26)	37 g/day (30 – 53)	77 g/day (53 – 244)
PLG (mmol/L)	5.8 (4.9 – 6.9)	5.8 (4.8 – 6.9)	5.8 (4.9 – 7.0)	5.8 (5.0 – 7.0)
No. participants	1,930	1,914	1,914	1,917
Model 1	ref.	0.99 (0.98, 1.01)	0.98 (0.97, 0.99)	0.98 (0.96, 0.99)
Model 2	ref.	0.99 (0.98, 1.00)	0.98 (0.97, 0.99)	0.98 (0.96, 0.99)
Model 3	ref.	0.99 (0.98, 1.00)	0.98 (0.97, 1.00)	0.98 (0.97, 1.00)
Fruit juice	2 g/day (0 – 5)	16 g/day (6 – 31)	72 g/day (32 – 129)	200 g/day (130 – 1,135)
PLG (mmol/L)	5.8 (4.9 – 6.9)	5.8 (4.9 – 7.0)	5.9 (5.0 – 7.0)	5.8 (4.9 – 6.9)
No. participants	1,940	1,950	1,884	1,901
Model 1	ref.	1.00 (0.99, 1.01)	1.00 (0.99, 1.02)	1.00 (0.98, 1.02)
Model 2	ref.	1.00 (0.99, 1.01)	1.00 (0.99, 1.02)	1.00 (0.99, 1.02)
Model 3	ref.	1.00 (0.99, 1.01)	1.00 (0.99, 1.02)	1.01 (0.99, 1.02)

Ratios of means and 95% CIs were obtained from the model with the exposure fitted as a continuous variable through a restricted cubic spline and are reported for the median intake in each quartile relative to the median intake in quartile 1. Model 1 adjusted for age and sex; Model 2 adjusted for age, sex, physical activity levels, level of education, SEIFA (socio-economical index for areas), income, BMI, smoking status, self-reported prevalence of cardiovascular disease, and parental history of diabetes; Model 3 adjusted for all covariates in Model 2 plus energy intake, and intakes (g/day) of alcohol, vegetables, red meat, and processed meat. Post load plasma glucose (PLG) is presented as median (interquartile range). Fruit and fruit juice intakes (g/day) are presented as median (range).

Table 3. Associations between fruit intake and estimates of pancreatic β-cell function and insulin sensitivity (n=7,675).

	Fruit intake quartiles			
	Q1	Q2	Q3	Q4
Serum insulin				
Total fruit				
Insulin (microunits/ml)	12.3 (9.6 – 16.9)	12.4 (9.4 – 16.3)	12.1 (9.5 – 15.9)	11.9 (9.1 – 15.3)
Model 1	ref.	0.99 (0.97, 1.02)	0.96 (0.93, 0.99)	0.94 (0.91, 0.97)
Model 2	ref.	0.99 (0.97, 1.02)	0.97 (0.95, 1.00)	0.95 (0.93, 0.98)
Model 3	ref.	1.00 (0.98, 1.02)	0.98 (0.95, 1.00)	0.96 (0.93, 0.98)
Apples				
Insulin (microunits/ml)	12.3 (9.5 – 16.5)	12.4 (9.5 – 15.8)	12.0 (9.3 – 15.8)	12.0 (9.3 – 15.6)
Model 1	ref.	0.99 (0.97, 1.02)	0.97 (0.95, 1.00)	0.95 (0.92, 0.98)
Model 2	ref.	0.98 (0.96, 1.00)	0.97 (0.95, 0.99)	0.96 (0.94, 0.98)
Model 3	ref.	0.98 (0.96, 1.00)	0.97 (0.95, 0.99)	0.97 (0.94, 0.99)
Oranges and other citrus				
Insulin (microunits/ml)	12.4 (9.6 – 16.5)	12.1 (9.4 – 16.2)	12.3 (9.4 – 16.1)	11.9 (9.3 – 15.4)
Model 1	ref.	0.98 (0.95, 1.01)	0.96 (0.94, 0.99)	0.95 (0.92, 0.98)
Model 2	ref.	0.98 (0.96, 1.00)	0.97 (0.95, 1.00)	0.97 (0.95, 1.00)
Model 3	ref.	0.98 (0.96, 1.00)	0.98 (0.96, 1.00)	0.97 (0.95, 1.00)
Bananas				
Insulin (microunits/ml)	12.3 (9.5 – 16.5)	12.3 (9.4 – 16.3)	12.0 (9.4 – 16.0)	12.1 (9.3 – 15.3)
Model 1	ref.	1.01 (0.99, 1.04)	0.97 (0.94, 0.99)	0.95 (0.92, 0.98)
Model 2	ref.	1.00 (0.98, 1.02)	0.98 (0.96, 1.00)	0.97 (0.95, 1.00)
Model 3	ref.	1.00 (0.98, 1.02)	0.99 (0.96, 1.01)	0.98 (0.95, 1.00)
Fruit juice				
Insulin (microunits/ml)	12.3 (9.5 – 16)	11.8 (9.3 – 16.1)	12.2 (9.4 – 16.0)	12.3 (9.5 – 16.0)
Model 1	ref.	1.01 (0.98, 1.03)	1.00 (0.97, 1.03)	1.00 (0.97, 1.03)
Model 2	ref.	1.01 (0.98, 1.03)	1.01 (0.99, 1.04)	1.02 (0.99, 1.04)
Model 3	ref.	1.01 (0.99, 1.03)	1.02 (0.99, 1.04)	1.03 (1.00, 1.05)
HOMA2 of β-cell function				
Total fruit				
HOMA2 B%	126.3 (105.2 – 152.1)	125.9 (105.0 – 152.0)	126.3 (107.0 – 150.2)	123.2 (103.0 – 147.6)
Model 1	ref.	1.00 (0.99, 1.02)	0.99 (0.97, 1.01)	0.97 (0.96, 0.99)
Model 2	ref.	1.00 (0.99, 1.02)	0.99 (0.98, 1.01)	0.98 (0.96, 1.00)
Model 3	ref.	1.00 (0.99, 1.02)	0.99 (0.98, 1.01)	0.98 (0.96, 1.00)
Apples				
HOMA2-%β	125.6 (104.7 – 152.3)	127.5 (107.2 – 152.2)	125.1 (105.0 – 149.9)	123.7 (102.9 – 147.4)
Model 1	ref.	1.00 (0.99, 1.02)	0.99 (0.98, 1.01)	0.98 (0.96, 0.99)
Model 2	ref.	0.99 (0.98, 1.01)	0.99 (0.98, 1.00)	0.98 (0.96, 1.00)
Model 3	ref.	0.99 (0.98, 1.01)	0.99 (0.97, 1.00)	0.98 (0.96, 1.00)
Oranges and other citrus				
HOMA2-%β	126.4 (105.9 – 151.4)	126.9 (105.4 – 150.7)	126.4 (105.3 – 151.3)	122.0 (102.3 – 148.3)
Model 1	ref.	1.00 (0.98, 1.01)	0.98 (0.97, 1.00)	0.97 (0.95, 0.99)
Model 2	ref.	1.00 (0.98, 1.01)	0.99 (0.97, 1.00)	0.98 (0.96, 1.00)
Model 3	ref.	1.00 (0.98, 1.01)	0.99 (0.97, 1.00)	0.98 (0.96, 1.00)

Bananas				
HOMA2-%β	124.9 (104.0 – 151.1)	126.4 (105.2 – 151.3)	126.2 (105.1 – 151.5)	124.6 (105.2 – 148.3)
Model 1	ref.	1.01 (1.00, 1.03)	1.00 (0.98, 1.01)	0.99 (0.97, 1.01)
Model 2	ref.	1.01 (1.00, 1.02)	1.00 (0.99, 1.02)	1.00 (0.98, 1.02)
Model 3	ref.	1.01 (0.99, 1.02)	1.00 (0.99, 1.02)	1.00 (0.98, 1.01)
Fruit juice				
HOMA2-%β	126.4 (105.5 – 150.8)	124.1 (103.8 – 149.3)	126.8 (105.4 – 151.2)	124.8 (104.0 – 149.9)
Model 1	ref.	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)	1.01 (0.99, 1.02)
Model 2	ref.	1.00 (0.99, 1.01)	1.01 (0.99, 1.02)	1.01 (1.00, 1.03)
Model 3	ref.	1.00 (0.99, 1.01)	1.01 (0.99, 1.02)	1.02 (1.00, 1.03)
HOMA2 of insulin sensitivity				
Total fruit				
HOMA2-%S	54.0 (39.6 – 69.5)	53.4 (40.7 – 70.5)	55.3 (42.1 – 69.8)	55.6 (43.4 – 72.6)
Model 1	ref.	1.00 (0.97, 1.03)	1.02 (0.99, 1.05)	1.05 (1.01, 1.08)
Model 2	ref.	1.01 (0.98, 1.03)	1.03 (1.00, 1.06)	1.06 (1.03, 1.09)
Model 3	ref.	1.01 (0.98, 1.03)	1.03 (1.00, 1.06)	1.05 (1.02, 1.08)
Apples				
HOMA2-%S	53.9 (40.1 – 69.6)	53.8 (40.6 – 69.9)	55.2 (42.5 – 71.5)	55.2 (42.6 – 71.3)
Model 1	ref.	0.99 (0.96, 1.02)	1.00 (0.98, 1.03)	1.02 (0.99, 1.06)
Model 2	ref.	1.01 (0.99, 1.04)	1.02 (1.00, 1.05)	1.04 (1.01, 1.07)
Model 3	ref.	1.01 (0.99, 1.04)	1.02 (1.00, 1.05)	1.03 (1.00, 1.07)
Oranges and other citrus				
HOMA2-%S	53.6 (40.4 – 69.2)	54.9 (41.3 – 71.0)	53.8 (41.1 – 71.0)	56.0 (43.4 – 71.0)
Model 1	ref.	1.00 (0.97, 1.03)	1.03 (1.00, 1.06)	1.06 (1.02, 1.09)
Model 2	ref.	1.01 (0.98, 1.04)	1.03 (1.00, 1.05)	1.05 (1.02, 1.08)
Model 3	ref.	1.01 (0.98, 1.04)	1.03 (1.00, 1.05)	1.05 (1.01, 1.08)
Bananas				
HOMA2-%S	3.6 (40.4 – 70.1)	54.1 (40.9 – 70.7)	55.1 (41.6 – 70.9)	55.0 (43.1 – 71.3)
Model 1	ref.	1.00 (0.97, 1.03)	1.03 (1.01, 1.06)	1.05 (1.02, 1.09)
Model 2	ref.	1.00 (0.98, 1.03)	1.03 (1.00, 1.06)	1.04 (1.01, 1.08)
Model 3	ref.	1.00 (0.98, 1.03)	1.03 (1.00, 1.05)	1.04 (1.01, 1.07)
Fruit juice				
HOMA2-%S	53.9 (41.5 – 70.9)	56.1 (1.6 – 71.5)	54.3 (41.6 – 70.3)	54.2 (41.6 – 70.0)
Model 1	ref.	0.99 (0.97, 1.02)	0.98 (0.95, 1.01)	0.98 (0.95, 1.01)
Model 2	ref.	1.00 (0.97, 1.02)	0.98 (0.96, 1.01)	0.97 (0.95, 1.00)
Model 3	ref.	1.00 (0.97, 1.02)	0.98 (0.95, 1.01)	0.97 (0.94, 1.00)

Ratios of means and 95% CIs were obtained from the model with the exposure fitted as a continuous variable through a restricted cubic spline and are reported for the median intake in each quartile relative to the median intake in quartile 1. Model 1 adjusted for age and sex; Model 2 adjusted for age, sex, physical activity levels, level of education, SEIFA (socio-economical index for areas), income, BMI, smoking status, self-reported prevalence of cardiovascular disease, and parental history of diabetes; Model 3 adjusted for all covariates in Model 2 plus energy intake, and intakes (g/day) of alcohol, vegetables, red meat, and processed meat. Insulin, HOMA2-%β and HOMA2-%S are presented as median (interquartile range).

Figure 1

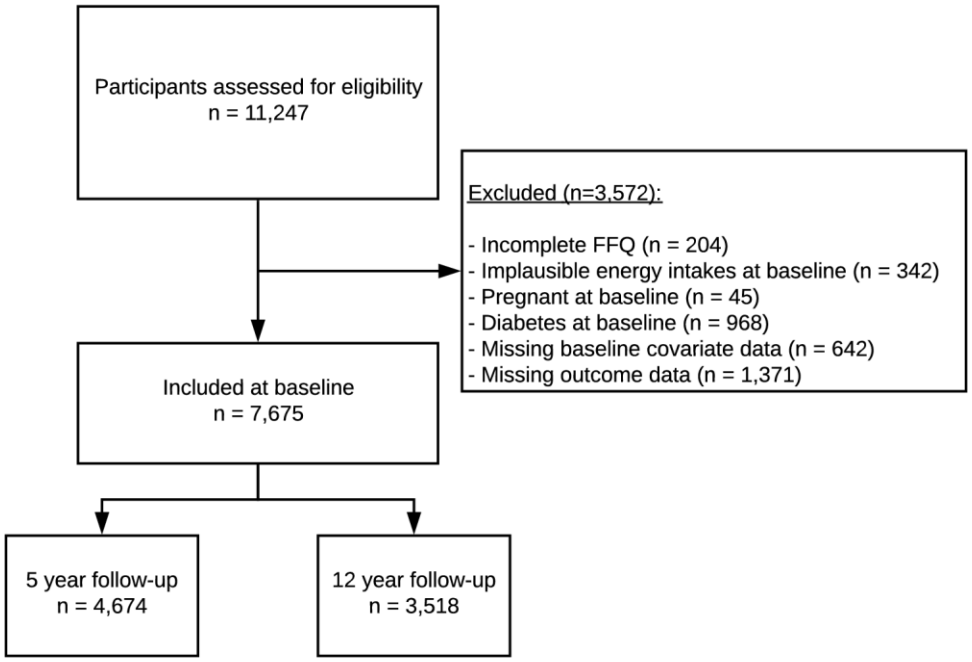

Figure 2

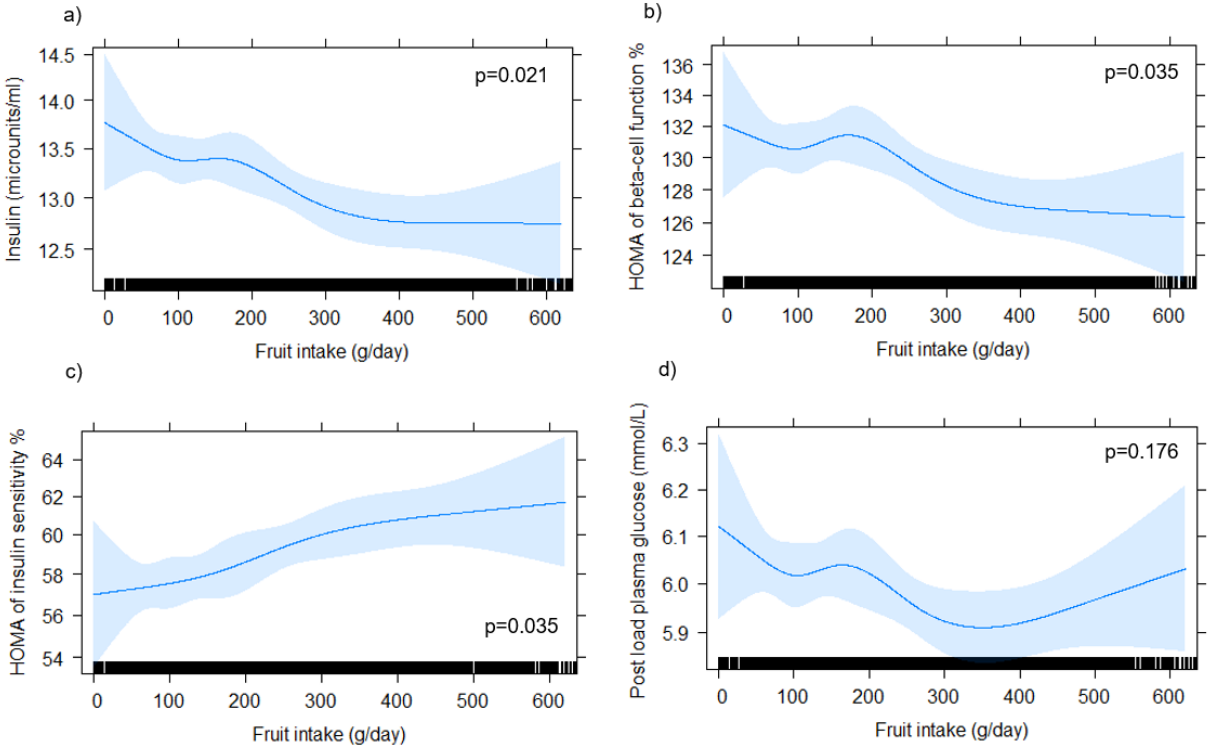

Figure 3