Prepregnancy adherence to plant-based diet indices and exploratory dietary patterns in relation to fecundability

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Abstract

Background—Modest associations have been reported between specific food groups or nutrients and fecundability [measured by time to pregnancy (TTP)]. Examining overall diets provides a more holistic approach towards understanding the relationships with fecundability. It is not known if plant-based diets indices or exploratory dietary patterns are associated with fecundability.

Objective—We examine the associations between adherence to (1) plant-based diet indices and (2) exploratory dietary patterns and fecundability among women planning pregnancy.

Design—Data were analysed from the Singapore S-PRESTO study. Pre-pregnancy diet was assessed using a semi-quantitative food frequency questionnaire from which the overall, healthful and unhealthful plant-based diet indices (oPDI, hPDI and uPDI) were calculated. Exploratory dietary patterns were derived using factor analysis based on forty-four pre-defined food groups. Participants were categorized into quintiles based on their dietary pattern scores. TTP (in menstrual cycles) was ascertained within a year of dietary assessment. Discrete-time proportional hazard models, adjusted for confounders, were used to estimate fecundability ratios (FRs) and 95% CIs, with FR>1 indicating a shorter TTP.

Results—Among 805 women, 383 pregnancies confirmed by ultrasound scans occurred. Compared to women in the lowest quintile, those in the highest quintile of the uPDI had reduced fecundability [FR of Q5 vs Q1 (95% CI): 0.65 (0.46, 0.91), p trend: 0.009]. Conversely, greater adherence to the hPDI was associated with increased fecundability [1.46 (1.02, 2.07), p trend: 0.036]. The oPDI was not associated with fecundability. Among the three exploratory dietary patterns, only greater adherence to the 'Fast Food and Sweetened Beverages' pattern (FFSB) was associated with reduced fecundability [0.61 (0.40, 0.91), p trend: 0.018].

Conclusions—Greater adherence to the uPDI or the FFSB dietary pattern was associated with reduced fecundability among Asian women. Greater adherence to the hPDI may be beneficial for fecundability, though this requires confirmation by future studies.

Keywords

Plant-Based Diet; Dietary patterns; Diet indices; Time-to-Pregnancy; Fecundability; Preconception

Abbreviations

(3DFD)	3-day food diary
(ART)	Assisted reproductive technology
(BLD)	Bread, Legumes and Dairy

(FFSB)	Fast Food and Sweetened Beverages
(FPMN)	Fish, Poultry/Meat and Noodles
(FFQ)	Food frequency questionnaire
(hPDI)	healthful plant-based dietary index
(HPG)	hypothalamic pituitary gonadal axis
(IGF-I)	insulin-like growth factor-I
(LMP)	last menstrual period
(oPDI)	overall plant-based dietary index
(PDIs)	Plant-based diet indices
(PCOS)	polycystic ovary syndrome
(TTP)	Time to pregnancy
(uPDI)	unhealthful plant-based dietary index

Introduction

There is a natural variability among women in their biological capacity to conceive (1). Fecundability, measured by the time to pregnancy (TTP), is the probability of a woman conceiving during one of her usual menstrual cycles (2, 3). Based on data across 190 countries, it is estimated that among married women aged 20 to 44 years, 1.9% and 10.5% of them had primary and secondary infertility, respectively (4). Locally, in Singapore, the time required to achieve a clinical pregnancy exceeds a year for about 15% of couples (5). Existing studies have reported modest associations between intakes of specific foods/beverages (such as dairy (6), seafood (7), diet soda and fruit juice (8)] or nutrients [such as total fat, specific types of fats and fatty acids (9), glycemic load, added sugar (10) and iron (11)]) and fecundability. However, studies examining overall diets, which takes into account the synergistic effects of individual dietary components on diet-fecundability associations, are limited.

Diet indices (index-based) and exploratory (empirically derived) dietary patterns have been commonly used to characterise the overall diets of populations (12). Greater adherence to diet indices such as the 'Pro-fertility' diet, Mediterranean diet or Preconception Dietary Risk (PDR) score, were associated with increased clinical pregnancy rates in women seeking to conceive using assisted reproductive technology (ART) (13–16). However, no published studies to date have examined diet indices with fecundability specifically as an outcome. While a vegetarian diet has been associated with reduced odds of primary ovarian insufficiency (17), higher intakes of animal protein (18) or dairy protein (19) have been associated with increased risk of ovulatory infertility and lower ovarian reserve, respectively. Collectively, these studies suggest the potential benefits of plant-based diets (an index-based

dietary pattern) to fecundability, such that an examination of the links between them is of interest.

To date, only two studies have examined the associations between pre-pregnancy exploratory dietary patterns; an 'Unhealthy diet' was associated with lower rates of clinical pregnancy among Iranian women (20) and the 'Mediterranean-type' dietary pattern with a lower odds of difficulty conceiving among Spanish women (21). Based on these studies, it remains unclear whether greater adherence to a healthy diet or limiting intakes of less healthy foods optimizes fecundability. Additionally, there remains a paucity of data in this area among Asian women.

Examining both index-based and exploratory dietary patterns have shown to be complementary in understanding diet-health outcome associations (22), with each approach having unique strengths (23). Taken together, we aimed to examine the associations between pre-pregnancy adherence to plant-based indices as well as exploratory dietary patterns and fecundability among a cohort of Asian women planning pregnancy. We hypothesized that women with greater adherence to a healthy plant-based or a 'healthy' exploratory dietary pattern would have increased fecundability.

Methods

Study population

The Singapore PREconception Study of long-Term maternal and child Outcomes (S-PRESTO) study is an ongoing prospective cohort study, which aims to examine the relationships of maternal exposures before conception and during pregnancy with subsequent maternal and offspring metabolic health outcomes (24). Between February 2015 and October 2017, non-pregnant women of Chinese, Malay, Indian ethnicity or any combination of these three ethnicities who planned to conceive within 1 year from recruitment and reside in Singapore for the next five years were enrolled. The exclusion criteria were as follows: (1) diagnosed with Type I or Type II diabetes, (2) have taken systemic steroids, anticonvulsants or sought treatment for Human Immunodeficiency Virus (HIV), Hepatitis B or C in the month prior to enrollment, (3) already pregnant at the first screening visit, (4) had already been trying to conceive for over 18 months and (5) have sought assisted fertility treatment (except clomiphene and letrozole) or undergone hormonal contraception treatment in the past month prior to enrollment. Further details of this study has been published (24). Written informed consent was provided by all participants. Ethical approval was obtained from the SingHealth Centralised Institutional Review Board (reference 2019/2143). This study has been registered at ClinicalTrials.gov (NCT 03531658).

In this study, we excluded women with missing information required to compute the time to pregnancy or those who were lost to follow up (n=81), were already attempting to conceive for more than a year at enrollment (n=137; who were likely to have pre-existing pathology underlying the subfertility) or who did not have dietary data (n=9) (Supplementary Figure 1). This leaves 805 women, with estimated energy intakes similar to the range typically reported, for the analysis.

Covariate assessment

At study enrollment, trained research staff conducted in-person interviews with participants and collected information including socio-demographic data (e.g. self-reported ethnicity), lifestyle behaviors (e.g. overall physical activity) (25) and anthropometry measures such as weight and height. Body mass index (BMI) is calculated by dividing weight (in kg) by squared height (in m^2). To assess their mental health, participants completed the Edinburgh Postnatal Depression Scale (EPDS) and State Trait Anxiety Inventory (STAI) questionnaires. We defined participants with EPDS scores of 13 as having probable depression, those with scores of >40 for the state anxiety subscale as having probable state anxiety (26).

Other information collected were related to the assessment of fecundability, including the number of months attempting to conceive at enrollment, usual length of menstrual cycle, date of last menstrual period (LMP), menstrual cycle regularity (irregular cycles defined as cycle lengths that varied by more than 5 days in the past 6 months) and self-reported diagnosis of polycystic ovary syndrome (PCOS).

Dietary assessment

A 92-item semi-quantitative, interviewer-administered food frequency questionnaire (FFQ) was used to assess participants' dietary intakes for the past month prior to study enrollment. Participants reported how often they consumed each food and beverage item in an open-ended format (ranging from never/rarely, frequency per month, frequency per week or frequency per day). Picture aids of various food portion sizes for items such as vegetables, poultry and standard-sized household tableware were used to help participants quantify the average amount consumed at each instance. A validation study on the exploratory dietary patterns derived using the FFQ against a reference dietary assessment method (3-day food diary- 3DFD) has been conducted (27). For this study, nutrient intakes from dietary supplements were not considered. However, in the sensitivity analyses, dietary supplement use (including vitamins, fish oil, minerals and any type of micronutrients) in the past three months prior to enrollment was considered.

Dietary patterns

Plant-based diet indices (PDIs)—In this study, we used three plant-based diet indices to assess diet quality: i) overall plant-based dietary index (oPDI), ii) healthful plant-based dietary index (hPDI) and iii) unhealthful plant-based dietary index (uPDI). The oPDI positively scores intakes of plant-based components (i.e. higher scores for higher intakes) and negatively scores intakes of animal-based ones (i.e. higher scores for lower intakes). While both the hPDI and uPDI negatively scores intakes of animal-based components, they differ in the scoring of plant-based foods; with the hPDI positively scoring intakes of healthy plant-based components (e.g. vegetables) and the uPDI positively scoring intakes of less healthy plant-based components (e.g. refined grains). The naming and selection of components of these indices were based on publications from existing prospective cohorts (28–30). Slight modifications were made so that they are applicable to the items captured by the FFQ administered in our study. We compared the PDI components used in our study with those from existing plant-based dietary indices and provided examples of the FFQ items included for each PDI component (Supplementary Table 1). The three PDIs

consisted of three main categories, with their 18 components: Healthy plant-based (n=7 components; whole grains, fruits, vegetables, nuts, legumes, vegetable oil and tea/coffee), Less healthy plant-based (n=6 components; fruit juice, refined grains, potatoes, sugar sweetened beverages, desserts/pastries & other vegetable fat (margarine)) and Animal-based (n=5 components; animal fat (butter), dairy/dairy products, egg, fish/seafood and meat/meat products).

The scoring of these 18 components was largely similar to that of the existing indices (28–30). Briefly, participants' intakes for each component were first ranked into quintiles (expressed in servings), which were assigned scores between 1 (lowest intake) and 5 (highest intake). To distinguish between women with no consumption and modest consumption within the lowest quintile (Q1) of each PDI component, those with no consumption were re-scored 0 (31). For the 'vegetable oil' component, the scoring was based on the two general questions on oil use as the FFQ administered did not specifically ask for the quantity of vegetable oil consumed. Participants were scored 1 point for the use of healthier oils (monounsaturated or polyunsaturated oil) and 0 point if none of these healthier oils was used. If more than one type of oil was listed as the most commonly used oil, an average score was calculated based on the oils listed. Alcohol consumption was considered separately as a potential covariate. Other vegetable fat (e.g. margarine) was included as part of the indices as we do not expect any changes in its fatty acid composition during data collection. The scores of all 18 PDI components were then summed, such that each participant had a score for the oPDI, hPDI and uPDI (with higher scores representing greater adherence to the respective diet indices). The PDIs (oPDI, hPDI and uPDI) have a theoretical range of 0 (lowest possible score) to 90 (highest possible score).

Exploratory dietary pattern scores—The FFQ items were first aggregated into forty-four pre-defined food groups before further analysis. Exploratory pre-pregnancy dietary patterns among the S-PRESTO women (n= 1007) have been identified in an earlier publication and were found to be reproducible in a subset (n=289) (27). In this study sample of 805 women, three dietary patterns were derived using exploratory factor analysis: Fast Food and Sweetened Beverages (FFSB), Bread, Legumes and Dairy (BLD) and Fish, Poultry/Meat and Noodles (FPMN) (Supplementary Table 2). Each participant had a dietary pattern score for each pattern (FFSB, BLD and FPMN) with higher scores representing greater adherence to that particular pattern.

Assessment of fecundability—The primary outcome was fecundability as measured by time to pregnancy (TTP). The associations between several preconception exposures (e.g. female adiposity, plasma glycemia and female sexual function) and fecundability has been examined in earlier publications (26, 32, 33). In this study, only natural conceptions resulting in clinical pregnancies were considered. These were assessed by positive urinary pregnancy tests and confirmed by ultrasound scans. For each woman, TTP (in discrete menstrual cycles) was first calculated to directly measure fecundability, as the outcome of interest. This was estimated as the total number of discrete cycles at risk of pregnancy over 1 year of follow-up using the following formula: [(number of days attempting to conceive before study entry / average menstrual cycle length) + (date of last menstrual period (LMP)

before conception or the most recent follow-up - date of LMP at study enrollment) / average menstrual cycle length)]. For women who achieved a clinical pregnancy, one more conception cycle was added. Further details on estimating the TTP can be found in previous publications (26, 32, 33).

Statistical analyses—We compared differences in baseline characteristics by quintiles of the PDIs (oPDI, hPDI and uPDI) and exploratory dietary pattern scores using chi-square tests for categorical variables and Kruskal Wallis tests for continuous variables. For all analyses, energy adjustment was performed only at the analysis stage to observe the effect of energy on the outcome measure and to facilitate interpretation of the results.

Discrete-time proportional hazards models were used to estimate fecundability ratios and their corresponding 95% confidence intervals [FR (95% CI)], representing the per cycle probability of conception in one group of women relative to a reference group. An FR of less than one indicates reduced fecundability (a longer TTP), while an FR of more than one indicates increased fecundability (a shorter TTP). The risk sets were based only on observed cycles at risk (i.e. pregnancy attempts during the study period) to account for left truncation. Censoring was applied if: (a) conception was not achieved after 12 months from study entry; (b) the participant was lost to follow-up or reported no longer trying to conceive; or (c) fertility treatment was initiated, whichever occurred first (33).

To examine the associations between the PDIs (oPDI, hPDI and uPDI) and fecundability, women were divided into quintiles for each PDI. Test for linear trends were conducted by using the median value of each quintile of the PDIs. Additionally, for each PDI, z-scores were calculated to compute the FR per standard deviation increase in the respective PDI. Confounding was evaluated using prior knowledge and the use of a directed acyclic graph. The final model (Model 1) included terms for energy, the two other dietary pattern scores, maternal age, maternal ethnicity, maternal highest educational attainment and cycle regularity. To assess if having had a previous birth modified the associations, Model 1A was additionally adjusted for parity. The same statistical methods and models were applied when examining the associations between pre-pregnancy adherence to each exploratory dietary pattern and fecundability. Additionally, we adjusted for gravidity (0, 1, and 2) instead of parity in Model 1A to determine if this had any effect on the estimates.

Spearman rank pairwise correlations between the PDIs and exploratory dietary pattern scores were computed to assess similarities between the two approaches used to derive dietary pattern scores. Concordance between the PDIs and exploratory dietary pattern scores were assessed by determining the proportions of participants cross-classified into the same quintiles, same or adjacent quintiles and opposite quintiles (34).

Sensitivity analyses were conducted to examine the robustness of the results. We examined if the significant associations (observed in Model 1) remained with additional adjustment for the following: [A] potential intermediates of BMI and glycemic status (normoglycemia or dysglycemia (diabetes and pre-diabetes) based on an oral glucose tolerance test with a 75g glucose load where plasma glucose levels at fasting and at 2 hour were measured), which were both shown to be associated with fecundability in earlier publications (32, 33); [B]

overall physical activity and [C] dietary supplement use. To test if the associations were robust, we conducted the analyses by excluding women with the following conditions: [D] polycystic ovary syndrome (PCOS) as these women are likely to take longer to achieve natural conception (35); [E] implausible menstrual cycle information to account for any potential misreporting; [F] considered only women who achieved live births (instead of confirmed pregnancy used in the primary analyses) as an outcome, which is typically examined in similar studies (36) and considered only women with no probable state anxiety and only those with no probable depression. Effect modification by maternal age, parity and maternal BMI were evaluated using cross product terms between each categorical characteristic and linear term of the respective dietary pattern scores. Data was analysed using STATA 14.2 (STATACorp, Texas). Statistical tests were two-sided and p values of less than 0.05 were considered to indicate statistical significance.

Results

Characteristics of the study population

Women in the highest quintiles of oPDI and hPDI were likely to be older, of higher educational attainment and were never smokers compared with those in the lowest quintiles (Table 1). Additionally, women in the highest quintile of the oPDI were likely to be of Indian ethnicity or parous than those in the lowest quintile. Women in the highest quintile of the hPDI were likely to be of Chinese or Indian ethnicity, had regular menstrual cycles and tended to consume dietary supplements than those in the lowest quintile. Conversely, women in the highest quintiles of the uPDI were likely to be of non-Chinese ethnicity and of lower educational attainment, were physically active, had shorter daily sitting times and were more likely to report symptoms of probable depression than those in the lowest quintile (Table 1). The characteristics of women belonging to the highest as compared with the lowest quintiles of the FFSB, BLD or FPMN patterns are shown in Supplementary Table 3. Notably, compared with women in the lowest quintile of the respective patterns, women in highest quintile of the FFSB pattern or uPDI shared similar characteristics.

A comparison of women in the study sample and those who were excluded showed that included women were likely to be younger, with higher educational attainment, ever consumed alcohol, never smokers, more physically active for the past week and had BMI within the normal range (Supplementary Table 4). Among 805 women, 383 pregnancies confirmed with ultrasound scans occurred.

Plant-based diet indices (PDIs)

In the study sample of 805 women, the observed scores for the PDIs were 24 to 73 (oPDI), 23 to 71 (hPDI) and 25 to 66 (uPDI), respectively. While a moderate positive correlation was observed between the oPDI and hPDI ($\rho= 0.47$), weak correlations were observed between the oPDI and uPDI ($\rho= 0.16$) and between the hPDI and uPDI ($\rho= -0.18$). In terms of their nutrient profiles, women in the highest quintile of the oPDI had higher intakes of energy, carbohydrates and dietary fiber, but lower protein intakes than those in the lowest quintile (Table 1). Those in the highest quintile of the hPDI had lower energy but higher dietary fiber intakes than those in the lowest quintile. Women in the highest quintile of the uPDI had

lower energy, protein, total fat and dietary fiber intakes, but higher intakes of carbohydrates than those in the lowest quintile.

Association between PDIs and fecundability

Women with the greatest adherence to the uPDI had reduced fecundability [FR for Q5 vs Q1 of uPDI: 0.65 (0.46, 0.91); FR for per SD increase in uPDI: 0.85 (0.77, 0.94), Model 1] and the association remained statistically significant upon adjustment for parity. Conversely, women with the greatest adherence to hPDI had increased fecundability [Q5 vs Q1 for hPDI: 1.46 (95% CI: 1.02, 2.07); per SD increase in hPDI: 1.12 (1.00, 1.26), Model 1]. However, this association was attenuated after additional adjustment for parity [Q5 vs Q1 of hPDI: 1.43 (95% CI: 1.00, 2.03), Model 1A]. No association was observed between oPDI and fecundability (Table 2).

Association between exploratory dietary patterns and fecundability

Women in the highest quintile of the FFSB pattern had reduced fecundability [Q5 vs Q1: 0.61 (95% CI: 0.40, 0.91); per SD increase in FFSB score: 0.83 (0.70, 0.99), Model 1] as compared with those in the lowest quintile. No association was observed between the BLD or FPMN patterns and fecundability (Table 2).

Correlation and concordance between PDIs and exploratory dietary patterns

Comparing the correlations between the PDIs and exploratory dietary patterns, the oPDI was moderately correlated to the BLD pattern ($\rho= 0.52$). The hPDI had a strong negative correlation ($\rho= -0.65$) with the FFSB pattern and the uPDI was moderately correlated to the FFSB pattern ($\rho= 0.44$) (Table 3). Similar trends were observed for concordance between the PDIs and exploratory dietary pattern pairs (Supplementary Table 5).

Sensitivity analyses

The associations between the dietary patterns (FFSB, uPDI and hPDI) and fecundability in (Model 1) were consistent with those in the primary analyses (Supplementary Figure 2, **Main**) when we additionally adjusted for potential intermediates of BMI and glycemic status (**A**), overall physical activity (**B**), dietary supplement use (**C**), excluded women with PCOS (**D**), excluded women with implausible menstrual cycle information (**E**) and considered only women who conceived and achieved live birth as an outcome (**F**) (Supplementary Figure 2, B–F). The exclusion of women with probable state anxiety or those with probable depression did not change the results appreciably (data not shown). Similarly, when we adjusted for gravidity instead of parity in Model 1A, there was little effect on the estimates (data not shown).

Discussion

In this cohort of Asian women planning pregnancy, greater adherence to the uPDI and FFSB dietary pattern were associated with reduced fecundability. The association between greater adherence to the hPDI and increased fecundability was attenuated after additional adjustment for parity. No significant association between adherence to the oPDI and other exploratory dietary patterns (BLD and FPMN) with fecundability was observed.

While the index-based PDIs and exploratory dietary patterns shared similarities (evident by their moderate correlations), they captured distinctive aspects of the overall diets among S-PRESTO women, highlighting the value of examining dietary patterns using both approaches.

Insulin resistance and inflammation (both involved in the pathology of Type II diabetes) are known to exert adverse effects on ovarian steroidogenesis (37). Given this plausible mechanism of action, our study findings on less healthy overall diets (uPDI and FFSB) and reduced fecundability are reminiscent of studies where the uPDIs were associated with increased risk of Type II diabetes (28, 31). While our finding on the FFSB pattern is in line with another study (20), it contradicts two previous studies (20, 21). In these studies, the 'Western diet' or the 'Western-type' dietary pattern' (both characterised by high intakes of sweetened drinks, fast foods and refined grains) were not associated with clinical pregnancy or odds of difficulty conceiving. Unlike these two studies that examined biochemical pregnancy (measured 12 days after embryo transfer) or difficulty in conceiving (experienced within a 2 year follow up period), we examined the time taken to achieve a clinical pregnancy from the onset of pregnancy intent. When fertility studies are conducted on populations with no known reports of infertility, it is important to recognise that there is an inherent variation in the length of the preconception period among individuals (2). In this regard, based on our findings, women planning pregnancy may consider limiting intakes of less healthy foods (both plant- and animal-based) to optimise the time taken to achieve pregnancy.

Although precise mechanisms underlying the associations between dietary intakes and fecundability have not been fully understood, the undisrupted ovarian steroidogenesis and optimal regulation of the hypothalamic pituitary gonadal axis (HPG) have been suggested to be important for reproductive success (37). Unhealthful plant-based diets have been associated with increased risks of metabolic diseases (such as Type II diabetes, cardiovascular diseases) (28, 31, 34) via potential mechanisms such as increased inflammation, which may partly explain the associations observed in this study. However, other biological pathways may be involved and future mechanistic studies are required.

Based on our study findings for the hPDI and oPDI, there is weak evidence to suggest that higher intakes of plant-based foods coupled with a reduction in animal-based ones are associated with increased fecundability. This is contrary to two studies where higher vegetable protein intakes were associated with reduced risks of ovulatory infertility among American nurses (18) and adherence to a vegetarian diet reduced risks of premature ovarian failure among Chinese women (17). The authors suggested that the anti-oxidative properties of a vegetarian diet reduced oxidative stress on oocytes, while higher intakes of animal proteins elevate circulating insulin-like growth factor-I (IGF-I), adversely affecting the ovaries and regulation of the HPG axis (17–19). In our study, further analyses demonstrated that higher intakes of healthy plant-based foods tended to be associated with increased fecundability [FR (95% CI) of Q5 vs Q1 for all healthy plant-based components: 1.37 (0.96, 1.97); all less healthy plant-based components: 0.74 (0.49, 1.13) and all animal-based components: 0.68 (0.44, 1.05)] but were not statistically significant (data not shown). These findings require further confirmation in future studies.

Concurring with a previous study where the 'Healthy' pattern was not associated with clinical pregnancy (20), we observed no association between the two other relatively healthy exploratory dietary patterns (BLD and FPMN) and fecundability. Conflicting findings between variants of the Mediterranean diet [e.g. Mediterranean diet index, Mediterranean diet score or 'Mediterranean-type' exploratory dietary pattern (13, 14, 16, 21)] and pregnancy rates highlights the need to utilise both dietary pattern approaches in a single setting to support any associations observed (38). In this study, moderately correlated PDI and exploratory dietary pattern pairs have largely similar associations with fecundability, thus strengthening our findings. There is currently a shift towards emphasising dietary patterns as reflected in the Dietary Guidelines for Americans (DGA) 2020-2025 and the Academy of Nutrition Sciences' position on the vital role of dietary patterns in developing food-based dietary guidelines (39, 40); studies like the current one could contribute to the emerging evidence base on preconception diets that can optimize fecundability.

Strengths of this study include the prospective measurement of fecundability to limit recall bias (41) and a detailed examination of dietary intakes using an FFQ. Given the absence of a single, superior approach to characterise overall diets (38), examining the associations of both diet indices and exploratory dietary patterns with fecundability is advantageous.

Several limitations need to be considered. First, dietary intakes were self-reported using a semi-quantitative FFQ. Nonetheless, in the absence of food or nutrient biomarkers, the FFQ is a widely used tool for examining diet-disease associations (38). While there could be misclassification of dietary intakes due to dietary changes that may have occurred after the baseline visit, this is likely to be non-differential by pregnancy status as fecundability was prospectively measured. Though the recall period of the FFQ is relatively short, this limits recall bias and enables more accurate reporting of dietary intakes as compared with having a longer recall period (42). Additionally, a number of studies have used the same recall period for their FFQs (43). In this study, within-person variation in dietary intakes is less of a concern since data from FFQ instead of the 3DFD was used (44). Similarly, seasonal variation in dietary intakes is unlikely in Singapore, where more than 90% of the food consumed locally is imported (45). Second, given the observational nature of this study, residual or unmeasured confounding may be present. For instance, data on paternal diet was not available for all women, thereby excluding the male dietary factor contribution to fecundability. However, similar studies have noted moderate to high correlations between couples' dietary intakes and showed that including the male factor did not materially change their findings (8, 46). Third, operational differences in the scoring of the PDIs may affect their ability to detect associations with outcomes (34). In this study, the 'Miscellaneous animal-based foods' component of existing PDIs was omitted as it was already accounted for in the other PDI components. However, it was deemed necessary to make slight modifications to the PDI scoring so that they were applicable to the items captured by the FFQ administered. Fourth, the generalisability of our results may be limited by the empirical derivation of dietary pattern scores. Moreover, the study sample is relatively younger (52% of women were less than 30 years) than the local female population since the highest age-specific fertility rate occurred among those aged 30 to 34 years (47). Nevertheless, the observed associations did not differ by maternal age. Fifth, acknowledging that the observed associations may be confounded by dietary supplement use, we additionally adjusted for this

in the final model (Model 1) and the findings remained largely similar. Sixth, information on conditions such as endometriosis, thyroid disorders that could affect fecundability was not collected. These conditions should ideally be included in our sensitivity analyses. Seventh, we did not collect information on participants' total sexual intercourse frequency for each menstrual cycle during follow up. Although enrolled women were encouraged to engage in sexual intercourse for 2 to 3 times per week, some may have temporarily ceased or delayed their attempts to conceive due to stressful lifestyles. This is reflected by the low pregnancy proportion (48%) in this study that is consistent with Singapore's low total fertility rate (47).

In conclusion, greater adherence to the uPDI or the FFSB dietary pattern was associated with reduced fecundability among Asian women. Findings from this study suggest that Asian women planning pregnancy may consider limiting intakes of less healthy plant and animal foods. However, future research is required to confirm these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Sources of support

Data availability

The data catalogue of the S-PRESTO study can be accessed on https://sicsdatavault.sg/#

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Secondary Abstract

Plant-based diets are increasingly popular as they are associated with reduced risks of chronic diseases and considered a sustainable diet for planetary health. Do these diets contribute to fecundability (as measured by time to pregnancy)?

Table 1

Baseline characteristics and selected nutrient intakes by quintiles of the plant-based diet indices

Characteristic [1]	Overall PDI (oPDI)		healthful PDI (hPDI)		unhealthful PDI (uPDI)	
	Q1	Q5	Q1	Q5	Q1	Q5
Number in each quintile	158	134	172	144	182	153
Median score (p25, p75)	38 (35, 40)	59 (57, 61) [3]	37 (33, 39)	56 (55, 59) [3]	36 (33, 37)	53 (52, 56) [3]
Age (years)						
< 30	97 (61.4)	61 (45.5) [3]	122 (70.9)	56 (38.9) [3]	94 (51.7)	81 (52.9)
30- 34	55 (34.8)	54 (40.3) [3]	44 (25.6)	65 (45.1) [3]	65 (35.7)	53 (34.6)
35	6 (3.8)	19 (14.2) [3]	6 (3.5)	23 (16) [3]	23 (12.6)	19 (12.4)
Ethnicity						
Chinese	111 (70.3)	89 (66.4) [3]	96 (55.8)	112 (77.8) [3]	150 (82.4)	87 (56.9) [3]
Malay	37 (23.4)	19 (14.1) [3]	60 (34.9)	8 (5.6) [3]	13 (7.1)	43 (28.1) [3]
Indian	9 (5.7)	24 (17.9) [3]	11 (6.4)	24 (16.7) [3]	18 (9.9)	20 (13.1) [3]
Mix	1 (0.6)	2 (1.5) [3]	5 (2.9)	0 (0) [3]	1 (0.5)	3 (2.0) [3]
Highest educational attainment						
Below Degree level	81 (51.3)	40 (29.9) [3]	90 (52.3)	30 (20.8) [3]	45 (24.7)	72 (47.1) [3]
Degree level and above	77 (48.7)	94 (70.2) [3]	82 (47.7)	114 (79.2) [3]	137 (75.3)	81 (52.9) [3]
Parity [2]						
Nulliparous	111 (70.7)	76 (56.7) [3]	118 (68.6)	95 (66)	116 (63.7)	103 (67.8)
Parous	46 (29.3)	58 (43.3) [3]	54 (31.4)	49 (34)	66 (36.3)	49 (32.2)
Alcohol consumption						
Never drinkers	47 (29.8)	44 (32.8)	61 (35.5)	40 (27.8)	60 (33)	53 (34.6)
Ever drinkers	111 (70.3)	90 (67.2)	111 (64.5)	104 (72.2)	122 (67)	100 (65.4)
Smoking status						
Never smokers	131 (82.9)	123 (91.8) [3]	141 (82)	140 (97.2) [3]	175 (96.2)	136 (88.9)
Active smokers	12 (7.6)	0 (0)	17 (9.9)	0 (0)	3 (1.7)	6 (3.9)
Previous smokers	15 (9.5)	11 (8.2) [3]	14 (8.1)	4 (2.8) [3]	4 (2.2)	11 (7.2)
Overall physical activity [2]						
Inactive	28 (17.8)	25 (18.7)	28 (16.4)	19 (13.2)	21 (11.6)	27 (17.7) [3]
Minimally Active	82 (52.2)	68 (50.8)	76 (44.4)	82 (56.9)	111 (61.3)	77 (50.3) [3]
Active	47 (29.9)	41 (30.6)	67 (39.2)	43 (29.9)	49 (27.1)	49 (32) [3]
Total sitting time (hours/day) [2]						
0 to 8	42 (26.9)	40 (29.9)	50 (29.6)	42 (29.2)	45 (24.9)	41 (27.2) [3]

Characteristic [1]	Overall PDI (oPDI)		healthful PDI (hPDI)		unhealthful PDI (uPDI)	
	Q1	Q5	Q1	Q5	Q1	Q5
8 to 11	50 (32.1)	40 (29.9)	52 (30.8)	48 (33.3)	59 (32.6)	49 (32.5) [3]
More than 11	64 (41)	54 (40.3)	67 (39.6)	54 (37.5)	77 (42.5)	61 (40.4) [3]
BMI (kg/m^2) [2]						
< 18.5	17 (10.8)	10 (7.5)	18 (10.5)	12 (8.3)	19 (10.5)	7 (4.6)
18.5- 24.9	93 (58.9)	90 (67.2)	96 (56.1)	98 (68.1)	115 (63.5)	102 (66.7)
>= 25	48 (30.4)	34 (25.4)	57 (33.3)	34 (23.6)	47 (26)	44 (28.8)
Glycemic status [2]						
Normoglycemia	139 (89.1)	113 (86.3)	151 (89.9)	128 (88.9)	165 (92.2)	129 (86)
Dysglycemia	17 (10.9)	18 (13.7)	17 (10.1)	16 (11.1)	14 (7.8)	21 (14)
Age at menarche (years) [2]						
< 12	34 (21.7)	44 (33.1)	46 (26.7)	38 (26.6)	46 (25.6)	40 (26.5)
12 to 13	81 (51.6)	62 (46.6)	89 (51.7)	86 (60.1)	93 (51.7)	86 (57)
> 13	42 (26.8)	27 (20.3)	37 (21.5)	19 (13.3)	41 (22.8)	25 (16.6)
Cycle regularity						
Irregular	61 (38.6)	43 (32.1)	67 (39)	40 (27.8) [3]	62 (34.1)	53 (34.6)
Regular	97 (61.4)	91 (67.9)	105 (61.1)	104 (72.2) [3]	120 (65.9)	100 (65.4)
Probable state anxiety						
Yes	32 (24.2)	26 (23.0)	28 (19.9)	28 (23.5)	38 (24.1)	31 (23.3)
No	100 (75.8)	87 (77.0)	113 (80.1)	91 (76.5)	120 (76.0)	102 (76.7)
Probable depression						
Yes	20 (15.0)	19 (16.7)	17 (12.0)	16 (13.3)	13 (8.1)	26 (19.4) [3]
No	113 (85.0)	95 (83.3)	125 (88.0)	104 (86.7)	147 (91.9)	108 (80.6) [3]
Dietary supplement use						
Yes	100 (63.3)	85 (63.4)	90 (52.3)	101 (70.1) [3]	126 (69.6)	94 (61.4)
No	58 (36.7)	49 (36.6)	82 (47.7)	43 (29.9) [3]	55 (30.4)	59 (38.6)
Food group intakes (servings/day)						
Whole grains	0.5 (0.6)	1.2 (0.9) [3]	0.4 (0.6)	1.2 (0.8) [3]	1.2 (1)	0.4 (0.4) [3]
Fruits	0.6 (0.7)	1.4 (0.9) [3]	0.7 (0.7)	1.4 (0.9) [3]	1.5 (1)	0.6 (0.7) [3]
Vegetables	1.1 (0.7)	2.2 (1.1) [3]	1.3 (0.8)	2.1 (1.1) [3]	2.3 (1.4)	1.1 (0.8) [3]
Nuts	0 (0)	0.1 (0.1) [3]	0 (0)	0.1 (0.1) [3]	0.07 (0.09)	0.02 (0.04) [3]
Legumes	0.1 (0.1)	0.3 (0.2) [3]	0.1 (0.2)	0.3 (0.2) [3]	0.3 (0.3)	0.2 (0.2) [3]
Vegetable oil	1.9 (2.4)	4 (2) [3]	1.8 (2.4)	4.3 (1.8) [3]	3.3 (2.4)	3.2 (2.4)
Tea and coffee	0.5 (0.7)	1.2 (0.9) [3]	0.6 (0.7)	1.1 (1.1) [3]	1.1 (1.2)	0.7 (0.6)
Fruit juice	0.1 (0.2)	0.3 (0.5) [3]	0.2 (0.3)	0.2 (0.4)	0.1 (0.2)	0.2 (0.3) [3]
Refined grains	3.4 (1.7)	4.4 (2.2) [3]	4.9 (1.9)	2.5 (1.2) [3]	3.2 (1.6)	4.4 (2.1) [3]

Characteristic [1]	Overall PDI (oPDI)		healthful PDI (hPDI)		unhealthful PDI (uPDI)	
	Q1	Q5	Q1	Q5	Q1	Q5
Potatoes	0.1 (0.1)	0.2 (0.1) [3]	0.2 (0.2)	0.1 (0.1) [3]	0.1 (0.2)	0.1 (0.1) [3]
Sugar sweetened beverages	0.3 (0.5)	0.5 (0.6) [3]	0.7 (1)	0.2 (0.2) [3]	0.3 (0.5)	0.5 (0.5) [3]
Desserts and Pastries	0.4 (0.4)	1.2 (0.9) [3]	1 (0.8)	0.6 (0.7) [3]	0.7 (0.8)	0.9 (0.8) [3]
Other vegetable fat (e.g. margarine)	0 (0.1)	0.2 (0.5) [3]	0 (0.2)	0 (0.1)	0 (0.1)	0.1 (0.4) [3]
Animal fat (butter)	0.1 (0.2)	0.2 (0.3) [3]	0.2 (0.4)	0.1 (0.3) [3]	0.1 (0.2)	0.1 (0.2) [3]
Dairy and dairy products	0.6 (0.5)	0.8 (0.6) [3]	0.8 (0.6)	0.6 (0.5) [3]	0.7 (0.6)	0.5 (0.4) [3]
Egg	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)	0.2 (0.2) [3]	0.3 (0.2)	0.1 (0.1) [3]
Fish or seafood	0.8 (0.6)	1.0 (0.7)	1.1 (0.7)	0.8 (0.6) [3]	1.1 (0.7)	0.7 (0.5) [3]
Meat and meat products	1.9 (1.5)	1.6 (1.1)	2.3 (1.4)	1.2 (0.7) [3]	1.9 (1.3)	1.5 (1.1) [3]
Daily nutrient intakes						
Energy (kcal)	1679 (675)	2525 (806) [3]	2331 (820)	1746 (500) [3]	2168 (742)	1888 (729) [3]
Carbohydrates (% En)	50 (8)	54 (5) [3]	51 (5)	52 (6)	49 (6)	54 (6) [3]
Protein (% En)	20 (4)	17 (3) [3]	19 (4)	18 (3)	20 (4)	17 (3) [3]
Total Fat (% En)	30 (5)	30 (4)	30 (4)	31 (4)	31 (4)	29 (4) [3]
Dietary Fiber (grams per 1000 kcal)	8 (2)	10 (2) [3]	8 (2)	12 (3) [3]	11 (3)	8 (2) [3]

[1] Categorical variables are presented as n (%). Continuous variables are presented as means (SDs) unless otherwise stated. Differences across quintiles were compared using chi-square tests for categorical variables and Kruskal-Wallis test for continuous variables (comparing mean ranks)

[2] Missing information for parity (n=1), overall physical activity (n=3), total sitting time (n=9), BMI (n=4), Glycemic status (n=11), age of menarche (n=8), probable state anxiety (n=123), probable depression (n=116), dietary supplement use (n=1)

[3] $P < 0.05$ for differences across quintiles for chi-square tests for categorical variables and Kruskal-Wallis test for continuous variables (comparing mean ranks)

Abbreviations: healthful PDI (hPDI); overall PDI (oPDI); unhealthful PDI (uPDI).

Table 2

Adjusted FRs and 95% CIs for fecundability according to quintiles of overall, healthful and unhealthful plant-based and exploratory dietary patterns

Plant-based dietary patterns	Number of pregnancies/ number of women	Total number of follow up cycles	FR (95% CI)			P trend [2]	FR per SD increase [2]
			Model 0 [1]	Model 1 [2]	Model 1A [3]		
Overall PDI							
Q1 (lowest adherence)	73/ 158	1527	1	1	1	0.420	1.02 (0.91, 1.14)
Q2	90/176	1640	1.15 (0.84, 1.58)	1.16 (0.85, 1.59)	1.16 (0.85, 1.59)		
Q3	90/192	1850	1.05 (0.77, 1.44)	1.03 (0.75, 1.42)	0.98 (0.71, 1.35)		
Q4	68/145	1431	1.04 (0.74, 1.46)	1.06 (0.75, 1.51)	1.02 (0.72, 1.46)		
Q5 (highest adherence)	62/134	1248	1.1 (0.77, 1.59)	1.15 (0.79, 1.68)	1.12 (0.77, 1.63)		
healthful PDI							
Q1 (lowest adherence)	72/172	1672	1	1	1	0.036 [4]	1.12 (1.00, 1.26) [4]
Q2	65/143	1353	1.11 (0.79, 1.56)	1.21 (0.86, 1.72)	1.16 (0.82, 1.64)		
Q3	82/171	1704	1.13 (0.83, 1.56)	1.24 (0.89, 1.73)	1.21 (0.87, 1.70)		
Q4	87/175	1647	1.21 (0.88, 1.66)	1.32 (0.94, 1.84)	1.31 (0.94, 1.83)		
Q5 (highest adherence)	77/144	1320	1.31 (0.94, 1.83)	1.46 (1.02, 2.07) [4]	1.43 (1.00, 2.03) [4]		
unhealthful PDI							
Q1 (lowest adherence)	97/182	1647	1	1	1	0.009 [4]	0.85 (0.77, 0.94)
Q2	81/162	1494	0.94 (0.70, 1.27)	0.95 (0.71, 1.28)	0.94 (0.70, 1.26)		
Q3	85/169	1594	0.91 (0.68, 1.21)	0.88 (0.66, 1.18)	0.87 (0.64, 1.16)		
Q4	62/139	1399	0.74 (0.54, 1.02)	0.74 (0.53, 1.02)	0.72 (0.52, 1.00)		
Q5 (highest adherence)	58/153	1562	0.64 (0.46, 0.89) [4]	0.65 (0.46, 0.91) [4]	0.66 (0.47, 0.92) [4]		
Exploratory dietary patterns							
Bread, Legumes and Dairy (BLD) pattern							
Q1 (lowest adherence)	79/161	1580	1	1	1	0.559	0.95 (0.79, 1.15)
Q2	80/161	1484	1.03 (0.76, 1.42)	0.98 (0.71, 1.34)	0.96 (0.7, 1.33)		
Q3	77/161	1587	0.92 (0.66, 1.29)	0.86 (0.62, 1.21)	0.85 (0.61, 1.19)		
Q4	70/161	1517	0.86 (0.59, 1.23)	0.8 (0.55, 1.16)	0.8 (0.55, 1.17)		

Plant-based dietary patterns	Number of pregnancies/ number of women	Total number of follow up cycles	FR (95% CI)			P trend [2]	FR per SD increase [2]
			Model 0 [1]	Model 1 [2]	Model 1A [3]		
Q5 (highest adherence)	77/161	1528	0.95 (0.61, 1.47)	0.89 (0.58, 1.39)	0.91 (0.59, 1.42)		
Fish, Poultry/Meat and Noodles (FPMN) pattern							
Q1 (lowest adherence)	76/161	1605	1	1	1	0.351	0.92 (0.77, 1.11)
Q2	79/161	1489	1.07 (0.76, 1.49)	1.03 (0.73, 1.46)	1.04 (0.66, 1.65)		
Q3	77/161	1467	1.04 (0.73, 1.49)	1.02 (0.71, 1.49)	1.01 (0.56, 1.81)		
Q4	77/161	1604	0.93 (0.64, 1.36)	0.91 (0.61, 1.34)	0.92 (0.53, 1.57)		
Q5 (highest adherence)	74/161	1531	0.9 (0.59, 1.38)	0.85 (0.55, 1.34)	0.86 (0.45, 1.63)		
Fast Food and Sweetened Beverages (FFSB) pattern							
Q1 (lowest adherence)	90/161	1496	1	1	1	0.018 [4]	0.83 (0.70, 0.99) [4]
Q2	75/161	1525	0.81 (0.60, 1.11)	0.83 (0.61, 1.13)	0.82 (0.60, 1.13)		
Q3	80/161	1478	0.89 (0.65, 1.22)	0.91 (0.67, 1.25)	0.92 (0.67, 1.26)		
Q4	74/161	1575	0.77 (0.55, 1.07)	0.74 (0.53, 1.04)	0.74 (0.53, 1.04)		
Q5 (highest adherence)	64/161	1622	0.63 (0.43, 0.93) [4]	0.61 (0.40, 0.91) [4]	0.62 (0.41, 0.93) [4]		

[1] Model 0: Plant-based dietary patterns: Adjusted for estimated daily energy intakes. A posteriori dietary patterns: Adjusted for estimated daily energy intakes and other two dietary patterns z scores (n=805)

[2] Model 1: Adjusted for Model 0 + maternal age, ethnicity, highest educational attainment, cycle regularity (n=805)

[3] Model 1A: Adjusted for Model 1 + parity (n=804 due to n=1 with missing parity data)

[4] FR (95% CI) were generated using discrete time proportional hazard models. Statistical significance indicated by p < 0.05

Abbreviations: Bread, Legumes and Dairy (BLD); Fast Food and Sweetened Beverages pattern (FFSB); fecundability ratio (FR); Fish, Poultry/ Meat and Noodles (FPMN); healthful PDI (hPDI); overall PDI (oPDI); standard deviation (SD); unhealthful PDI (uPDI).

Table 3

Spearman rank correlation coefficients between PDIs and exploratory dietary

	Bread, Legumes and Dairy Pattern (BLD)	Fish, Poultry/Meat and Noodles pattern (FPMN)	Fast Food and Sweetened Beverages pattern (FFSB)
Overall PDI (oPDI)	052 [1]	025 [1]	-0.04
Healthful PDI (hPDI)	0.12 [1]	-0.03	-0.65 [1]
Unhealthful PDI (uPDI)	-0.20 [1]	-0.35 [1]	0.44 [1]

[1] P < 0.05 for Spearman correlation coefficients between the PDIs and exploratory dietary patterns.

Abbreviations: Bread, Legumes and Dairy (BLD); Fast Food and Sweetened Beverages pattern (FFSB); Fish, Poultry/Meat and Noodles pattern (FPMN).