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Title: Dietary potato intake and risks of type 2 diabetes and gestational diabetes mellitus

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Abstract:

Background & aims: Evidence regarding associations between potato consumption and type 2 diabetes (T2D) and gestational diabetes mellitus (GDM) risks is accumulating. This study aims to synthesize the evidence by conducting a meta-analysis of available studies.

Methods: PubMed, Web of Science, EMBASE and Cochrane Library were searched (up to August 2020) to retrieve all eligible studies on the associations of interest. The risk estimates with 95% confidence intervals (CIs) were summarized using random- or fixed-effects model based on heterogeneity. Meta-analyses were performed for East and West regions separately. Dose-response relationship was assessed using data from all intake categories in each study.

Results: A total of 19 studies (13 for T2D; 6 for GDM) were identified, including 21,357 T2D cases among 323,475 participants and 1,516 GDM cases among 29,288 pregnancies. Meta-analysis detected a significantly positive association with T2D risk for total potato (RR: 1.19 [1.06, 1.34]), baked/boiled/mashed potato (RR: 1.08 [1.00, 1.16]), and French fries/fried potato (RR: 1.33 [1.03, 1.70]) intakes among Western populations. Dose-response meta-analysis demonstrated a significantly increased T2D risk by 10% (95% CI: 1.07, 1.14; *P* for trend<0.001), 2% (95% CI: 1.00, 1.04; *P* for trend=0.02) and 34% (95% CI: 1.24, 1.46; *P* for trend<0.001) for each 80 g/day (serving) increment in total potato, unfried potato, and fried potato intakes, respectively. As for GDM, summarized estimates also suggested a higher though non-significant GDM risk for total potato (RR: 1.19 [0.89, 1.58]), and French fries/fried potato (RR: 1.03 [0.97, 1.09]) intakes in Western countries. In the dose-response meta-analysis, a significantly increased GDM risk was revealed for each daily serving (80g) intakes of total potato (RR: 1.22; 95% CI: 1.06, 1.42; *P* for trend=0.007) and unfried potato (RR: 1.26; 95% CI: 1.07, 1.48; *P* for trend=0.006).

Conclusions: This study suggests that higher potato intake is associated with higher T2D risk among Western populations. The positive relationship presents a significant dose-response manner. Wisely controlled potato consumption may confer potential glucometabolic benefits.

Keywords:

Potato intake, Type 2 diabetes, Gestational diabetes mellitus, Meta-analysis

Abbreviations:

T2D, type 2 diabetes; GDM, gestational diabetes mellitus; GI, glycemic index; GL, glycemic load; RR, relative risk; OR, odds ratio; HRs, hazard ratios; CIs, confidence intervals; BMI, body mass index; NOS, Newcastle-Ottawa Scale; FFQ, food frequency questionnaire; DAGS, direct acyclic graphs.

1. Introduction

The prevalence of type 2 diabetes (T2D) has reached the epidemic level globally [1]. It is projected that one-tenth of people will suffer from this condition by 2030 [2]. Meanwhile, gestational diabetes mellitus (GDM), a hyperglycemia clinical entity first diagnosed during pregnancy [3], affects almost 17.0 million births (13.2%) worldwide in 2019 [2]. As T2D and its numerous complications predispose individuals to cardiovascular diseases and premature deaths [1], GDM *per se* could translate into inter-generational adverse health outcomes including increased T2D risk for both mothers and offspring, forming a vicious cycle [4]. Given the substantial relevance of GDM with T2D and their similar pathophysiologic process [5], it would be intriguing and crucial to clarify possible common risk factor for both diseases. We envisage that widespread prevention of T2D and GDM could consequentially decrease the huge worldwide health/economic burden in total [6]. In both dysglycemia conditions, lifestyle factors and dietary habits have been elucidated as important modifiable determinants of risk [7, 8]. Yet, more research is still needed to further examine relevant agents that bear public health significance.

Potatoes, one of the most popular staple foods, provide a significant proportion of energy in many cultures' diet [9]. In the U.S. National Guideline of Healthy Eating (MyPlate) and Special Supplemental Nutrition Program for Women, Infants, and Children (WIC), potato is rather grouped as a vegetable [10, 11]. Potatoes can, admittedly, be a good source of key nutrients including potassium, vitamin C, and magnesium [12]. However, unlike other vegetables such as green leafy vegetables and legumes that offer overt health benefits, the role of potato consumption in human health still lacks consensus [13]. It is critical that potato primarily contains starches, the intake of which in general leads to a high glycemic index (GI) and glycemic load (GL) [13, 14]. And a high GI/GL diet is an established risk factor for both T2D and GDM [15, 16]. Evidence linking potato intake with risks of T2D and GDM has been

accumulating over the past decade; however, both the magnitude and direction of their reported estimates vary widely and greatly [17-20]. A recent meta-analysis of cohort studies concluded that higher total potato intake was associated with an increased risk of T2D; however, the likely divergent estimates for potato subtypes and the heterogeneity of association in different subgroups were not examined [21]. The distribution of potato intake levels differs substantially among different geographical regions. The highest potato intake levels in low potato intake countries are equal to low-moderate potato intake levels in high potato intake countries. It is, therefore, imperative that further and elaborate synthesis of the current evidence be performed, in an effort to dissect the ambiguous literature and also communicate the health message to healthcare practitioners, policymakers, and the general public (especially the high-risk population and women of childbearing age).

Herewith, we aimed to comprehensively summarize the results from studies examining the association of habitual potato consumption and the risks of T2D as well as GDM, using a dose-response meta-analysis approach. We also examined the possible variations in effect estimates by different potato types and other baseline variables.

2. Methods

2.1 Data sources and search

We conducted a systematic literature search for relevant studies examining the associations between potato intake and the risks of T2D and GDM. The electronic databases MEDLINE through PubMed (January 1950 - August 2020), ISI Web of Science (January 1956 - August 2020), EMBASE (January 1947 - August 2020), and Cochrane Library (January 1945 - August 2020) were searched based on the query syntax in the Supplemental Methods (Online Search Strategy). Publication language was not restricted. To identify additional studies, we further manually screened the references cited by retrieved articles and relevant reviews. Experts in

the field were also contacted to identify any unpublished or ongoing studies.

2.2 Study selection

The following criteria were applied to select eligible studies: 1) the study was a cohort, case-control or cross-sectional design; 2) the outcome of interest was T2D or GDM; 3) main exposures were potato (unspecified), baked, boiled or mashed potato, or French fries or fried potato; 4) hazard ratios (HRs), relative risks (RRs), or odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were available, or can be derived; and 5) multivariable adjustment was performed in statistical analyses. Studies did not clearly distinguish potatoes from other tubers were excluded. When multiple reports from the same study were identified, we used the results with the most complete and/or recently updated data. Two authors (F.G. and Q.Z.) independently screened all studies by title or abstract and then by a full-text evaluation using a standardized approach. Any disagreements were resolved by group discussions with senior investigators (L.M.).

2.3 Data extraction and quality assessment

The following data were extracted from each eligible study: the first author, publication year, country of origin, study name, follow-up duration (for cohort studies), participant characteristics (age, gender, and body mass index [BMI]), number of participants and events/cases, dietary assessment tool, categories of potato consumption, outcome ascertainment method, diagnostic criteria, risk estimates with corresponding 95% CIs, and covariates adjusted. For studies that provided several effect estimates, we extracted the estimates from the full multivariable model. When a study only provided estimates for individual potato food with specified cooking methods, we pooled data for specific potato foods. And when calculating the study estimate for total potatoes, we combined the subtype-specific estimates with those for total potatoes in other studies. If studies reported potato intake in servings or times per day, week, or month, the value was converted into grams per day (g/d)

based on the portion size specified in the publications [18, 22]. Otherwise, we assumed that the serving size was 80 g for all potato foods [23]. Leading authors were contacted for information that was incomplete or not reported.

We also extracted the key indicators of study quality and assessed the risk of bias according to the Newcastle-Ottawa Scale (NOS) [24]. This scale is composed of items of the quality of studies based on the following 3 aspects: selection of study groups (4 items), comparability (1 item), and ascertainment of exposure or outcome (3 items). A "star system" (range: 0-9) is utilized, with a higher score representing a higher quality. Studies with a score of 0-4, 5-7, or 8-9 points were considered as being of low, moderate, and high quality, respectively. All data were independently extracted and evaluated by two authors (F.G. and Q.Z.) using an electronic form, with discrepancies resolved through discussion.

2.4 Data synthesis and analyses

We pooled risk estimates and 95% CIs from each contributing study. Heterogeneity between studies was determined with Cochran's Q test and quantified by I^2 statistic. In case a significant heterogeneity existed (P<0.10 or I^2>50%), the pooled estimates were calculated using a random-effects model; otherwise, a fixed-effects model was appropriately chosen. Forest plots were utilized to visually assess the effect estimates and corresponding 95% CIs across studies. In view of the notable geographical difference in dietary cultures, we evaluated the region-specific (West & East) association for T2D and GDM outcomes, respectively. In the present study, we adopted the definition of culture that considers East Asia and the Middle East as Eastern countries; Russia, Europe, the Americas, Australia and New Zealand as Western countries [25].We also examined specific associations for individual potato foods, including baked, boiled or mashed potatoes and French fries or fried potatoes), since cooking processes and ingredients added during cooking may play a role in the associations of interest [26]. In addition, subgroup analyses by study design (cohort *vs.* case-control or cross-sectional), gender

(female *vs.* male *vs.* both), BMI status (<25 kg/m^2 *vs.* ≥25 kg/m^2), number of cases (<1000 *vs.* ≥1000), dietary factor adjustment (yes *vs.* no), study quality (moderate *vs.* high), as well as duration of follow-up (for cohort study: <10 years *vs.* ≥10 years) were conducted for potato-T2D association. As for GDM outcome, potential moderators including maternal age (<30 years *vs.* ≥30 years), pre-pregnancy BMI status (<25 kg/m^2 *vs.* ≥25 kg/m^2), incidence rate (<8% *vs.* ≥8%), timing of diet assessment (pre-pregnancy *vs.* peri- or during-pregnancy), and adjustment for parity (yes *vs.* no) were explored.

To evaluate the dose-response relationships between potato consumption and T2D as well as GDM, we first allocated the midpoint (median/mean level) of potato intake to each study arm (the term 'study arm' refers to the various intake categories shown in original articles). In the case of open-ended categories, the consumption was calculated by assuming the width of interval to be the same as the adjacent category. For binary intake variables, we assigned a score of 0.8*cutoff point to the lower category, and 1.2*cutoff point to the higher category, as suggested by Berlin et al [27]. Then, we calculated the covariance of risk estimates using the number of events and participants in each study arm and used the inverse of variance/covariance matrix as study weight in the parametric analysis [28]. If numbers of participants and cases were not provided, we used the average number of cases and participants in each category (total participants or cases divided by the number of categories) [18, 29]. A 2-stage hierarchical regression model was applied to conduct the dose-response meta-analysis (Stata MKSPLINE and GLST commands) [30, 31].

Finally, sensitivity analyses were performed by sequentially removing one study at a time and recalculating the pooled estimates to evaluate whether the results were significantly influenced by a single study. If the removal of any study either changed the significance level of summary association or altered the nominal effect size by 10% or more, it was deemed as being influential. Potential publication bias was evaluated with a visual inspection of funnel

plots and quantitative Egger's and Begg's regression tests (each significant at $P<0.10$). If publication bias was detected, we applied trim and fill method to test the number of "missing" studies and adjust the summary estimates. A two-sided *p*-value of less than 0.05 was considered statistically significant. All statistical analyses were conducted by using STATA software (version 10.2; STATA Corp., College Station, TX, USA).

3. Results

Our search strategy resulted in 8,657 potentially relevant citations (3,130 from PubMed, 2,381 from ISI Web of Science, 2,109 from EMBASE, and 1,037 from Cochrane Library), of which 2,010 duplicates were initially excluded (**Figure 1**). After screening titles and abstracts, 6,524 records were further removed, leaving 123 articles retrieved for full-text review. Of note, the study of Villegas et al. (2007) who reported the T2D risk associated with potato intake quintiles, was excluded due to unavailability of 95% CIs of the point estimates [32]. Finally, 16 full-text articles that met the inclusion criteria, together with 1 additional record identified by manual search, contributed to the quantitative synthesis in our meta-analysis (19 studies in total: 13 for T2D and 6 for GDM).

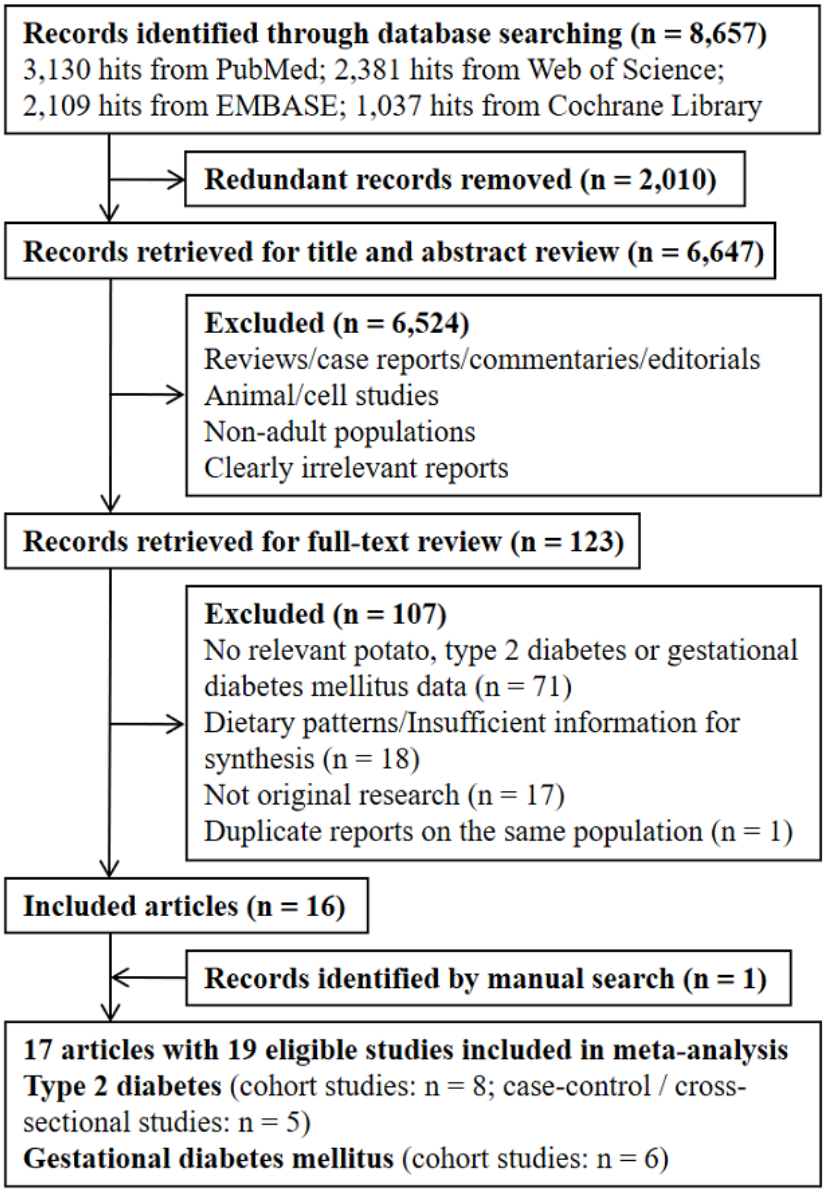

Figure 1. Flow diagram of literature search and screening

3.1 Study characteristics

The 13 identified studies concerning T2D (8 prospective cohort [17, 18, 22, 29, 33, 34], 1 case-control [35], and 4 cross-sectional studies [36-39]) included a total of 323,475 participants and 21,357 T2D cases (**Table S1** and **Table S2** in the Supplement). Among these studies, eight populations were from Western countries (Finland, the United States, Australia, Germany, and United Kingdom), and three were from Eastern countries (China, Iran, and Saudi Arabia). Besides one hospital-based case-control study and four volunteer-based (i.e., nurses and health

professionals) cohort studies, all other studies were population-based including general population from the study area. Nine studies enrolled both sexes, three consisted exclusively of women, and one included only men. The duration of follow-up in cohort studies ranged from 4 to 26 years. T2D was self-reported and then confirmed in six studies, whereas other studies identified cases by either linking health-care department records or assessing blood samples. Food intake was measured through food frequency questionnaire (FFQ) in 11 studies and dietary history interview in 2 studies. Potato consumption varied substantially across study populations, with the highest categories of potato intake ranged from 55.5 g/d to 339.6 g/d. Established risk factors for T2D were adjusted in the multivariable models, including age (n=13), BMI (n=11), family history of diabetes (n=11), energy intake (n=7), physical activity (n=9), smoking (n=7), alcohol drinking (n=7), other dietary factors (n=8), and gender (n=9). The quality assessment ratings for T2D studies were presented in **Table S4** and **Table S5**. The study-specific quality scores ranged from 5 to 9, with eleven studies being rated as high quality.

The 6 studies pertaining to GDM were all cohort studies [19, 20, 40-43], among which two papers have focused on the same population but examined different potato types [20, 40]. An overview of the study characteristics is shown in **Supplementary Table S3.** In total, 1,516 GDM cases and 29,288 pregnancies were involved. Of these studies, three populations were from Western countries (the United States and Iceland), and three were from Eastern countries (China and Iran). While one study included nurses as the population, other studies were hospital-based to recruit participants. All publications were written in English, except for the one in Chinese [43]. The average age of mothers ranged from 26.7 to 32.8 years old. The length of follow-up duration ranged from 1 to 12 years. GDM diagnosis was all confirmed in the maternal medical records. While five studies applied FFQ to measure food intake, one used 4-day weighed food records. Three studies assessed pre-pregnancy (previous year) habitual consumption of potatoes, but three other ones concerned peri-conception or during-pregnancy

dietary intakes. Their potato consumption levels showed a large variance, ranging from 25.7 g/d to 128.6 g/d in the highest intake group. Commonly adjusted covariates and potential confounders in each multivariable model included age (n=6), pre-pregnancy BMI or weight (n=5), family history of diabetes (n=5), energy intake (n=5), physical activity (n=4), other dietary factors (n=5), and parity (n=2). **Table S6** provided the quality assessment details for GDM studies and all 6 studies were rated as high quality (≥8 score).

3.2 Association between total potato intake and T2D

Of the 13 studies regarding the association between potato consumption and T2D risk, eight were from Western countries, among which 7 studies observed a positive association but only 4 of them reached statistical significance. Summary of the effect estimates for Western populations generated a significant 19% increase in T2D risk for higher total potato intakes (RR: 1.19 [1.06, 1.34]; **Figure 2**), with modest heterogeneity (I^2=43.7%; P=0.09) detected. Five studies were conducted in Eastern countries. Of them, 3 studies reported a significantly inverse effect estimate, yet the other two were in the positive direction. In contrast with Western populations, a non-significant overall estimate for T2D risk associated with potato consumption (RR: 0.94 [0.71, 1.25]; **Figure 2**) was observed among Eastern populations, with substantial between-study heterogeneity (I^2=92.1%; P<0.001). Then, the linear dose-response analysis suggested a significant 10% increase in T2D risk for per 80 g/day (approximately one serving) increase in total potato intake (RR: 1.10 [1.07, 1.14]; P for trend<0.001; P for non-linearity=0.14; **Figure 3**).

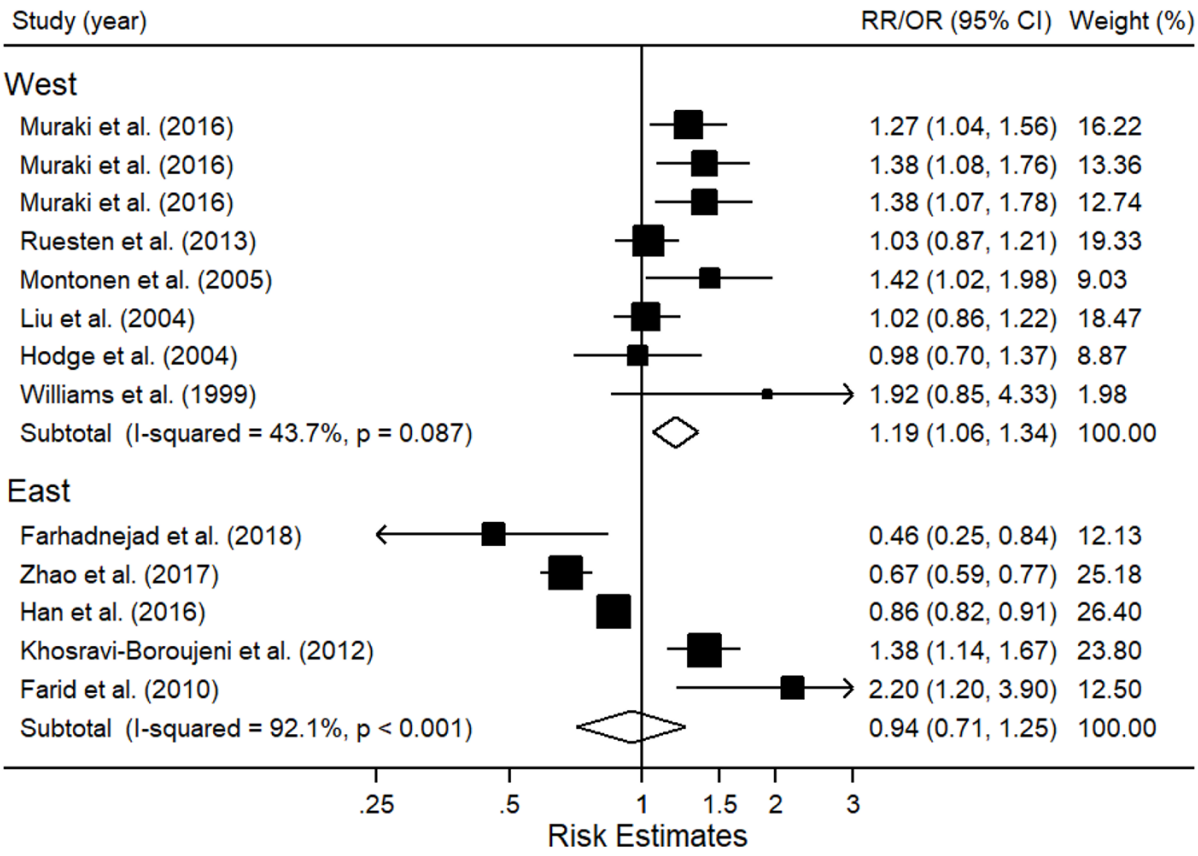

Figure 2. Forest plot of type 2 diabetes risk associated with total potato intake for West & East geographical regions based on random-effects meta-analysis. Squares represent study-specific risk estimates (RR/ORs), with the size reflecting their statistical weight. The diamond represents the pooled effect size with 95% confidence interval (CI). The percentage of heterogeneity due to between-study variation is shown by I^2 value.

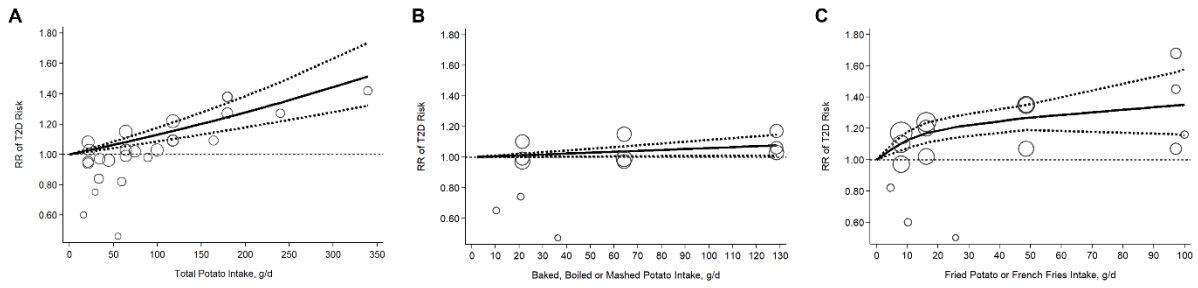

Figure 3. Dose-response analysis for associations of type 2 diabetes risk with total potato intake (**A**; *P* for trend<0.001; *P* for non-linearity=0.14), baked/boiled/mashed potato intake (**B**; *P* for trend=0.02; *P* for non-linearity=0.84), and fried potato/French fries intake (**C**; *P* for trend<0.001; *P* for non-linearity<0.001) in prospective cohort studies. Solid lines represent weighted relative risk on all data points; dashed lines are the corresponding 95% confidence interval. Size of circle is proportional to its statistical weight.

3.3 Association between individual potato foods and T2D

Five studies reported the association between consumption of baked, boiled or mashed potatoes and risk of T2D, and two of them was statistically positive [34]. When limiting the meta-analysis in Western countries, the synthesized effect size was marginally significantly positive (RR: 1.08 [1.00, 1.16], *P* =0.06; **Figure 4**) with little between-study heterogeneity (I^2=0.0%; *P*=0.37). Rather, for Eastern countries, the association was non-significantly negative using a random-effects model (RR: 0.84 [0.29, 2.40]; **Figure 4**). Then, the analytical model based on all intake categories from each study showed a significantly positive linear dose-response relation between baked, boiled or mashed potato consumption and T2D risk (RR for per 80 g/d increment: 1.02 [1.00, 1.04]; *P* for trend=0.02; *P* for nonlinearity=0.84; **Figure 3**).

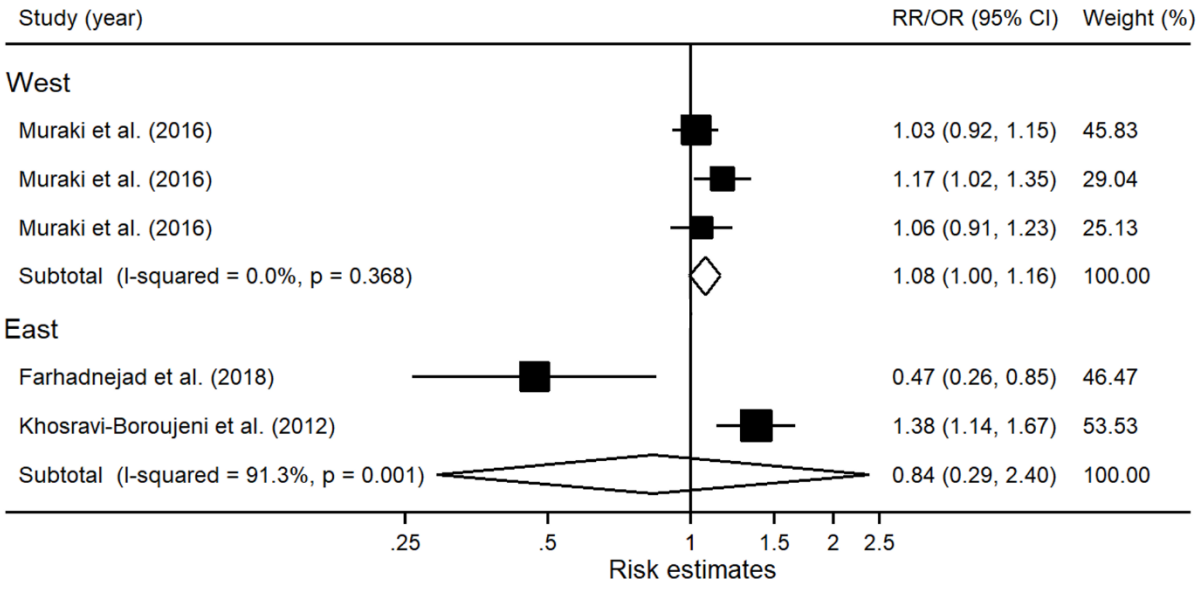

Figure 4. Forest plot of type 2 diabetes risk associated with baked, boiled or mashed potato intakes for West & East geographical regions based on random-effects meta-analysis. Squares represent study-specific risk estimates (RR/ORs), with the size reflecting their statistical weight. The diamond represents the pooled effect size with 95% confidence interval (CI). The percentage of heterogeneity due to between-study variation is shown by I^2 value.

Six studies examined the relationship between intake of fried potatoes or French fries and the risk of developing T2D [17, 34], of which two studies reported a significantly elevated risk [17]. The pooled RR for T2D comparing extreme intake categories among Western studies was

significantly positive (RR: 1.33 [1.03, 1.70]; **Figure 5**) with moderate heterogeneity detected (I^2=57.9%; P=0.07). By contrast, the summary risk estimate for Western countries lacked statistical significance (RR: 1.07 [0.25, 4.55]; **Figure 5**) and showed great heterogeneity (I^2=89.6%; P=0.002). In the dose-response meta-analysis, significant nonlinearity was detected (P for non-linearity<0.001; **Figure 3**), with an also significant 34% increase in T2D risk for each 80 g/day increment in fried potato or French fries intake (RR: 1.34 [1.24, 1.46]; P for trend<0.001).

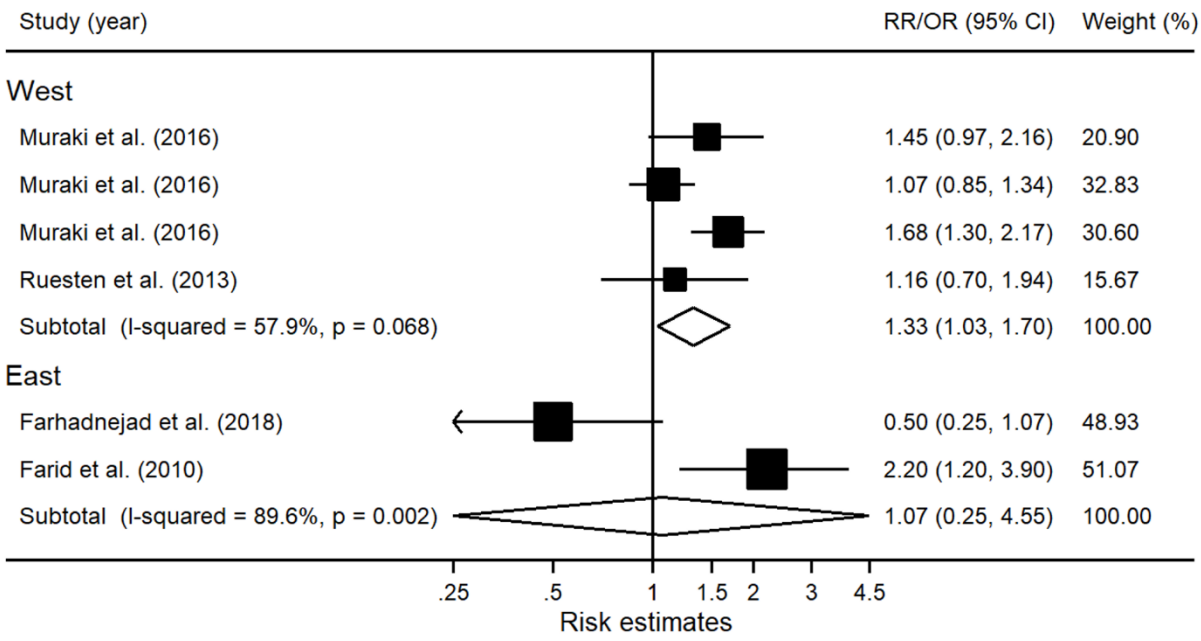

Figure 5. Forest plot of type 2 diabetes risk associated with French fries or fried potato intakes for West & East geographical regions based on random-effects meta-analysis. Squares represent study-specific risk estimates (RR/ORs), with the size reflecting their statistical weight. The diamond represents the pooled effect size with 95% confidence interval (CI). The percentage of heterogeneity due to between-study variation is shown by I^2 value.

3.4 Association between total potato intake and GDM

Among the cohort studies on the analysis of total potato (or its subtype) intake with risk of GDM, three were performed in Western countries. Summary of the studies conducted in Western countries yielded a positive effect size (RR: 1.19 [0.89, 1.58]; **Figure 6**) despite lack of statistical significance. While, the overall association for Eastern populations was non-

significant with a quite wide CI (RR: 0.84 [0.41, 1.72]; **Figure 6**) given significant heterogeneity (I^2=79.8%; *P*=0.03). By further fitting the restricted cubic spline model, we found a linear dose-response relation between total potato exposure and GDM incidence (*P* for nonlinearity=0.95): for each 80 g/day increase in total potato intake, the risk of GDM was heightened by 22% (RR: 1.22 [1.06, 1.42]; *P* for trend=0.007; **Figure 7**).

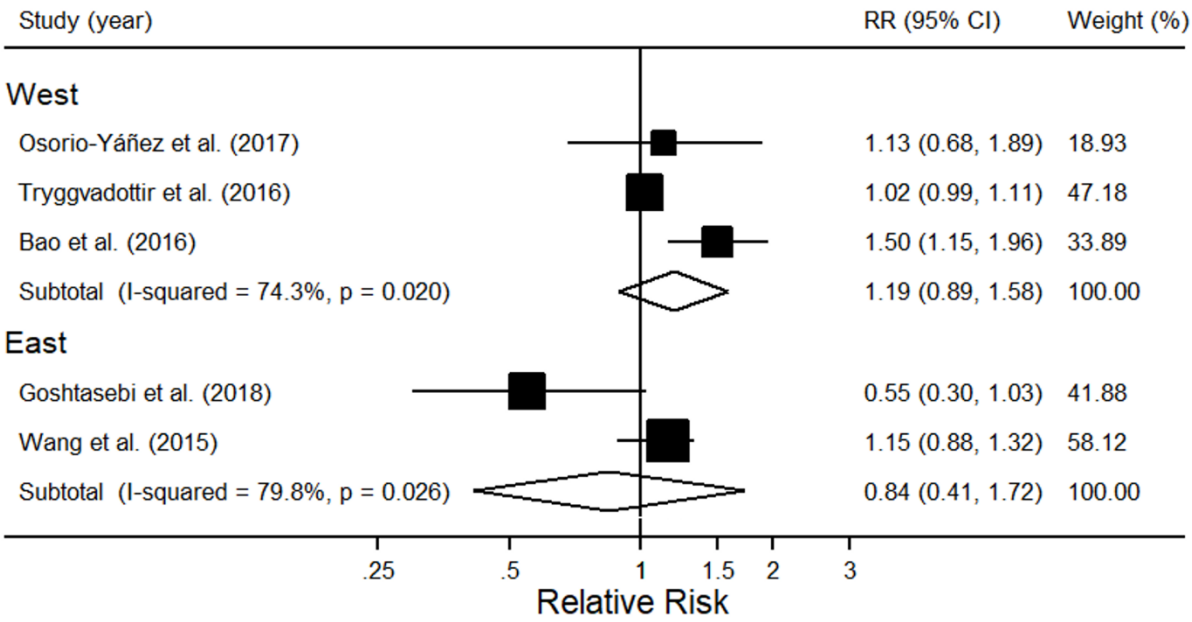

Figure 6. Forest plot of gestational diabetes risk associated with total potato intake for West & East geographical regions based on random-effects meta-analysis. Squares represent study-specific relative risks (RRs), with the size reflecting their statistical weight. The diamond represents the pooled RR with 95% confidence interval (CI). The percentage of heterogeneity due to between-study variation is shown by I^2 value.

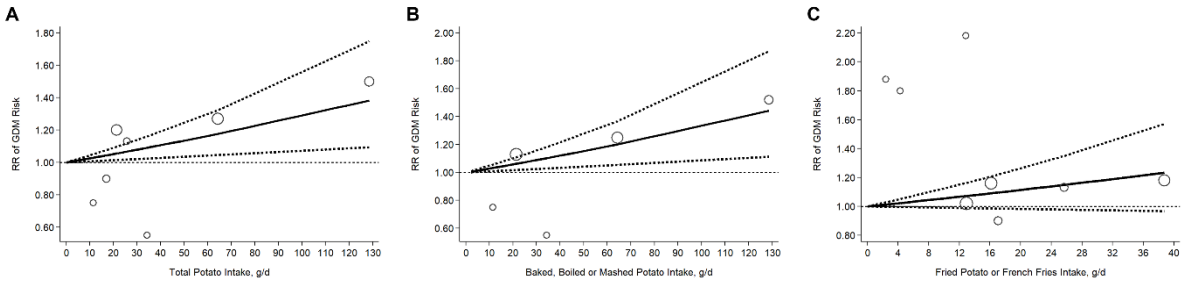

Figure 7. Dose-response analysis for associations of gestational diabetes risk with total potato intake (**A**; *P* for trend=0.007; *P* for non-linearity=0.95), baked/boiled/mashed potato intake (**B**; *P* for trend=0.006; *P* for nonlinearity=0.96), and fried potato/French fries intake (**C**; *P* for trend=0.09; *P* for non-linearity=0.69) in prospective cohort studies. Solid lines represent weighted relative risk on all data points; dashed lines are the corresponding 95% confidence interval. Size of circle is proportional to its

statistical weight.

3.5 Association between individual potato foods and GDM

Of the six studies identified, only two studies specifically reported the association between baked, boiled or mashed potato intakes and the GDM risk. Of them, one estimate from the US was statistically positive [19], while the other from Iran was non-significantly negative [20]. The limited number of studies restrained us from generating specific summary estimates for West/East areas. Then, the linear dose-response analysis did show a significant 26% increase in GDM risk for per 80 g/d increment in baked, boiled or mashed potato consumption (RR: 1.26 [1.07, 1.48]; *P* for trend=0.006; *P* for nonlinearity=0.96; **Figure 7**).

Four prospective studies evaluated the association between French fries or fried potato exposure and the maternal risk of GDM [19, 40-42]. Three of them were conducted among Western populations reporting a non-significantly positive relationship. Meta-analysis of these results also showed an increased yet non-significant risk of GDM for the West group (RR: 1.03 [0.97, 1.09]; I^2=0.0%; *P* for heterogeneity=0.53). Further, testing for dose-response using all included studies showed a 54% (RR for per 80 g/d: 1.54 [0.93, 2.54]; *P* for trend=0.09), albeit lacking statistical significance, increase in the risk of GDM for every serving increment of fried potato intake (*P* for nonlinearity=0.69; **Figure 7**).

3.6 Subgroup and sensitivity analyses

Subgroup analyses for potato-T2D association did not show significant effect modification by study deign, gender, BMI, number of cases, adjustment for dietary factors, or study quality (all *P* for meta-regression>0.05; **Table 1**). Nevertheless, the median length of follow-up was detected as a significant moderator, partly explaining the between-group heterogeneity among cohort studies (*P* for meta-regression=0.02). Compared with studies of shorter follow-up durations (RR: 0.95 [0.79, 1.15]), those with follow-up of ≥10 years pooled a significantly positive association of potato intake with T2D risk (RR: 1.34 [1.19, 1.52]). Sensitivity analyses

by removing each study from the synthesis did not alter the significance or direction of association.

In the subgroup analyses regarding GDM, none of the proposed moderators including demographic and study-specific methodological variables seemed to modify the pooled effect estimate significantly (all *P* for meta-regression>0.05; **Table 2**). Of particular note, a positive association between potato intake and GDM risk was significantly shown in the subpopulation of an advanced maternal age (RR: 1.41 [1.12, 1.79]) or with a normal pre-pregnancy weight (RR: 1.25 [1.08, 1.46]), but not in their younger or overweight counterparts. Sensitivity analyses showed that excluding any single study would not qualitatively change the overall results.

3.7 Publication bias

For potato-T2D meta-analysis, visual inspection of potential publication bias using a funnel plot demonstrated evidence of slight asymmetry around the central measure of pooled effect (**Figure S1**). Although the *Begg's* test was non-significant (*P*=0.86), the *Egger's* tests stood marginally significant (*P*=0.04) showing the presence of publication bias. Then, the trim-and-fill procedure was performed to detect the probably missing studies and thereby counteract such bias (**Figure S2**). By recalculating the overall estimate based on both the observed and the 2 imputed studies, we found that the corrected estimate (RR: 1.05 [0.90, 1.23]) did not alter the significance of association with only limited attenuation of the original effect size (RR: 1.10 [0.94, 1.30]). For potato-GDM meta-analysis, the funnel plot was visually symmetric, and neither the *Begg's* (*P*=0.81) nor *Egger's* tests (*P*=0.72) suggested the statistical evidence of publication bias (**Figure S3**).

4. Discussion

4.1 Summary of the findings

In this comprehensive meta-analysis, we included 19 observational studies providing quantitative estimates of the associations between habitual intake of potato foods and risks of T2D as well as GDM. The region-specific summary estimates consistently showed a more pronounced positive association of potato and its subtype intakes with T2D risk in Western countries. Then, the dose-response meta-analysis yielded a 10% and 22% increase in risks of T2D and GDM, respectively, for every 80g/day increment in total potato intake. For individual potato types, stronger positive associations were found for consumption of fried potatoes/French fries with T2D risk.

4.2 Relation to previous epidemiological evidence

This meta-analysis, so far as we know, is the first to review and pool the existing evidence for potato intake and the GDM risk. Moreover, we identified more eligible studies and conducted more detailed analyses than the previous meta-analysis work on the T2D outcome [21, 44]. Not surprisingly, there exist striking connections between GDM and T2D, with respect to etiopathogenesis (reduced insulin sensitivity alongside inadequate insulin secretion) and risk factors [5, 45]. Therefore, by examining the T2D and GDM outcomes simultaneously, our study could contribute to a more comprehensive overview of potato food consumption involved in the development of hyperglycemia diseases.

The findings of this meta-analysis are mostly in line with previous literatures. In general, the studies conducted among Western populations and those focusing on Western dietary patterns (cooked potato included) have showed that intake of potatoes or French fries could relate positively to insulin resistance, T2D, and GDM risks [38, 46, 47]. On the contrary, a population-based prospective study of 64,227 Chinese women observed a moderately reduced T2D risk for higher potato intake quintiles [32]. These results are consistent with our findings of a potentially harmful impact of potato consumption on T2D and GDM outcomes; however, the strength of the association of potato intake with T2D appeared to be slightly stronger for

Western populations than that for Eastern populations. The difference between Eastern and Western populations could be due to potato intake, cooking methods or dietary patterns. In particular, daily potato intake among Chinese ethnic group in New York population was reported to be 2 to 3 times lower than that among other racial subgroups [48], which is also supported by our analysis that the average intake level of potatoes was 43.5 g/d in Eastern countries and 100.8 g/d in Western countries. These inconsistent associations may be explainable by the distinct ways in which the potatoes are typically prepared. In most Western countries, potatoes are consumed as staple, with nearly two-thirds of them deep-fried as French fries, potato chips, and/or other processed products [49]. In China and similar Eastern countries, stir-fry cooking is the common cooking methods for potatoes [50]. In addition, it is likely that numerous foods may have interactive or synergistic effects on glucose metabolism. As a staple food consumed in Eastern countries, refined grain was associated with a higher risk of T2D; therefore, it is possible that the true adverse effects of potato were masked by dietary patterns with high intake of refined grain potentially [51]. Further research is warranted to clarify the associations across populations and to elucidate the underlying mechanism.

4.3 Potential mechanisms

The overall unfavorable effect of potato consumption on a diabetic state in the dose-response manner is biologically plausible. As a starch-rich food, hot instant potatoes can have a high GI at the range of 70 to 100 [52]. In the Western diet, potatoes are primarily served or consumed hot as a staple food and are therefore a significant contributor to total GL [9]. A high-GI or GL diet has been accused as an important risk factor for T2D and GDM development [16, 53]. The postprandial hyperglycemia induced by habitual consumption of high-GI food, could over-stimulate insulin secretion, induce oxidative stress and inflammatory injury to pancreatic β cells, as well as cause glycosylation of key enzymes responsible for glucose homeostasis, thereby leading to β-cell dysfunction or exhaustion and, in the long run, occurrence of T2D [54,

55]. As for GDM, pregnancy in its own right is a stressor to the maternal blood glucose metabolism, formulating a certain degree of insulin resistance and fasting hyperinsulinemia, so as to ensure adequate energy supply for the fetus development [56]. Hence, the gestation period should be a sensitive window when food with a high GI, compared to low GI, could tip the natural balance and contribute to a mother's propensity for developing GDM [16, 57]. Notably, our subgroup finding of a larger effect size among mothers of advanced maternal age indicates that they may be more susceptible to the unfavorable impact of high potato consumption. Evidence from animal models of rats also showed that feeding a high glycemic diet can detrimentally affect parameters of glucose homeostasis [58].

Furthermore, high potato diets could cause T2D through a potential mechanism of lipotoxicity. About five hours after consuming high-GI potatoes, low metabolic fuel state in vivo can trigger a counter-regulatory hormone response to maintain euglycemia, via activating gluconeogenic pathways and increasing free fatty acid concentrations [55]. This would reduce insulin-stimulated glucose uptake in target tissue, exacerbate insulin resistance and thus lead to glucose intolerance [59]. Another mechanism that could contribute to an elevated risk of T2D and GDM is that potatoes, as a tuber plant, might contain more toxic metals such as cadmium (Cd) than other most-consumed vegetables [60]. These toxic metals might disrupt enzymes kinetics and glucose uptake, result in dysfunction of the pancreatic β-cell, and increase oxidative stress and inflammatory markers, which thereby propel an individual toward a dysglycemia and hyperglycemia health outcome (viz., developing T2D and GDM), especially among the genetically predisposed population [61, 62].

In addition to those direct hypotheses regarding glucose metabolism, a likely candidate agent that mediates the unfavorable effects of potato consumption on T2D or GDM risk is weight gain. By following up a population of 120,877 American adults, Mozaffarian et al. demonstrated a modestly direct association between an increased daily serving of potatoes and

4-year weight gain (1.28lbs) [63]. It is possible that habitually excessive potato consumption could further undermine glucose metabolism, impair insulin sensitivity and subsequently, increase the risk of T2D or GDM occurrence through promoting weight gain [64, 65]. What striking in our results is the magnitude of total potato impact from subgroup analyses: stronger significantly-positive estimates for T2D and GDM were consistently shown in the subpopulation with a baseline BMI or pre-pregnancy BMI <25kg/m^2; in contrast, the associations of interest were neutral among the overweight or obese strata. By referring to the direct acyclic graphs (DAGs) tool to guide our causation assuming a true mediator effect of higher BMI, weight stratification (adjustment) in this scenario might in part neutralize the total unadjusted risk estimate to the direct effect size or cause a collider-stratification bias (viz., selection bias arising as a result of conditioning on a shared effect) [66, 67]. Simply put, some unmeasured exposure interactions with the intermediate variable may be introduced to override or cover the effects of potato consumption on diabetes in the overweight subgroup.

Our current study suggested that the associations were heterogeneous between intake of different potato foods in that the positive association was largely stronger for fried potatoes/French fries. It has been demonstrated that frying with oil can significantly increase the energy density of potatoes even though they have a relatively lower GI and higher resistant starch/fiber content than other cooked variants [26]. For example, large baked potatoes could contain approximately 300 calories, whereas energy intake from fried potatoes with a similar portion size may double [68]. In addition, in Western countries partially-hydrogenated oils that contain a substantial amount of *trans* fat were widely used to fry foods, including potatoes, before the use of *trans* fat was phased out in the past decade. *Trans* fat intake was clearly associated with an increased risk of T2D in humans [69]. As for the non-significant dose-response relationship between fried potato and GDM risk, a premature explanation goes that sophisticated cooking methods (e.g., vacuum frying or using enriched oils) may be specially

applied to minimize the side effects of French fries and potato chips for the sake of a healthy pregnancy [70]. Further studies are warranted to establish the underlying discrepant mechanisms.

4.4 Strengths and limitations

In the current study, we conducted a comprehensive and detailed meta-analysis of the associations by a wide variety of potential moderators. Of particular importance is the divergent findings for West and East regions, which could provide insights for researchers to further examine such intriguing differences and convey more straightforward message to readers. Moreover, the dose-response analysis enabled us to examine the shape of this relationship and the linear association between potato consumption and outcome risk lent further support to the causal interpretation.

On the other hand, this meta-analysis has some limitations that are worth discussing. First, certain synergistic or antagonistic effect may exist among different dietary components (i.e., accompanying or substituting food items). Although we considered effect estimates from the full multivariable model, we could not rule out the influence of potential synergistic effects of potato and food items on T2D and GDM risks. Second, most studies relied on FFQs to assess the intake of potatoes, which could have introduced measurement error and misclassification. However, most included studies are of a prospective design, where measurement errors in dietary assessments are more likely to be non-differential and therefore attenuate true associations toward the null. Third, only a limited number of eligible studies were identified for both disease outcomes, and even fewer studies had particularly distinguished specific potato cooking methods (i.e., fried *vs.* unfried potatoes); this subsistent issue to some degree restricted our power when interpreting the summary results. Hence, our meta-analysis should be a call for more well-designed studies from different populations who may prepare or consume potatoes differently across the globe, which not surprisingly, will contribute to a better and

profound knowledge of the relationship between potato intake and incidence risk of T2D and GDM. Lastly, although we detected low amount of publication bias in the potato-T2D meta-analysis, possibly due to the exclusion of study without variance estimates, the trim and fill technique evidenced that the impact of such bias on the overall results was rather limited.

4.5 Implications and recommendations

Evidence from the current meta-analysis, though still limited, suggests that habitual high intake of potato foods may predispose individuals to a higher risk of developing T2D and GDM. Nevertheless, caution should be exercised when interpreting our findings. Considering potato has been an affordable and the most popular staple food for many hundreds of years, it is impractical and inexpedient to kick out the potato, otherwise nutritious food (e.g., a good source of minerals and vitamins), from the daily diet. As the previous research discussed, the GI and nutrient content (e.g. phenolic compounds) of potatoes are substantially associated with the cooking techniques [26] and potato cultivars [71]. Specifically, deep-frying the potatoes may compromise the diet quality by introducing excess calories and unhealthy trans fatty acids, acrylamide, lipid oxidation and degradation compounds [72, 73]. In addition, the consumption strategy also plays a role. Chilled potatoes compared to boiled potato, and co-consumption of food such as broccoli compared to potato served alone, would positively impact glycemic response and improve glucose homeostasis [74, 75]. By contrast, high-fat toppings such as butter, cheese, and bacon bits, can substantially add excess calories to potato diets, resulting in increased chance of weight gain and diabetes onset.

From the perspective of public health practitioners, we suggest that instead of simply restricting the intake servings of potatoes, health policymakers should take steps to synthesize the lines of evidence and consensus from multiple disciplines (including nutrition epidemiology and food science), and make elaborate as well as targeted recommendations on the wise consumption of potato foods for the general public and those at high risk, so as to

optimize the nutritional status of the whole populations and abate the burden of hyperglycemia and other metabolic diseases.

5. Conclusion

In summary, the present meta-analysis of observational studies shows that higher intake of potato foods (especially fried potatoes/French fries) in the West is associated with a higher risk of T2D and GDM in a dose-response manner. Our findings indicate that potatoes, despite their plant origin, may not confer the same health benefits as other vegetables or healthful sources of carbohydrates, such as whole grains [17]. More well-designed prospective studies with long follow-up duration are needed to further elucidate this association in other populations, as well as the role of different cooking or preparing methods in the health effects of potato intake on glucometabolic health.

Author Contributions: LM and FG participated in project conception and development of research methods; LM obtained funding and provided oversight; FG and QZ did literature review and data extraction; FG and HJ performed the analyses; FG and LWT interpreted the results; FG and QZ drafted the manuscript; all authors contributed to critical revision of the manuscript.

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Appendix A. Supplementary data: Supplementary data related to this article can be found at XX.

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Table 1 Association between potato intake and risk of T2D by subgroups

Subgroup	No. study populations	Risk estimate (95% CI)	*P*-value	
			Heterogeneity	Meta-regression
Overall	13	1.10 (0.94, 1.30)	<0.001	NA
Study design				
Cohort	8	1.14 (0.98, 1.32)	0.01	0.98
Case-control/cross-sectional	5	1.10 (0.82, 1.47)	<0.001	
Region [a]				
West	9	1.19 (1.06, 1.34)	0.09	0.22
East	5	0.94 (0.71, 1.25)	<0.001	
Gender				
Female	3	1.20 (1.00, 1.44)	0.09	
Male	1	1.38 (1.07, 1.78)	NA	0.49
Female & Male	9	1.03 (0.85, 1.26)	<0.001	
BMI on average				
<25kg/m^2	4	1.34 (1.18, 1.53)	0.77	0.15
≥25kg/m^2	6	0.97 (0.71, 1.34)	<0.001	
No. of cases				
<1,000	6	1.15 (0.84, 1.56)	0.003	0.70
≥1,000	6	1.04 (0.85, 1.28)	<0.001	
Adjusted for dietary factors				
Yes	8	1.16 (0.94, 1.44)	<0.001	0.59
No	5	1.04 (0.75, 1.42)	<0.001	
Study quality [b]				
Moderate	2	1.42 (0.67, 2.99)	0.01	0.47
High	11	1.08 (0.90, 1.28)	<0.001	
Follow-up duration [c]				
<10 years	4	0.95 (0.79, 1.15)	0.09	0.02
≥10 years	4	1.34 (1.19, 1.52)	0.92	

BMI, body mass index; CI, confidence interval; NA, not applicable; T2D, type 2 diabetes.

[a] West region included countries such as Finland, the United States, Australia, Germany, and United Kingdom; East region included countries such as China, Iran, and Saudi Arabia.

[b] Study quality was assessed based on Newcastle-Ottawa Scale.

[c] Stratified analysis by follow-up duration was conducted for cohort studies only.

Table 2 Association between potato intake and risk of GDM by subgroups

Subgroup	No. study populations	Relative risk (95% CI)	*P*-value	
			Heterogeneity	Meta-regression
Overall [a]	5	1.10 (0.90, 1.34)	0.01	NA
Region [b]				
West	3	1.19 (0.89, 1.58)	0.02	0.82
East	2	0.84 (0.41, 1.72)	0.03	
Maternal age				
<30 years	3	1.01 (0.83, 1.23)	0.08	0.17
≥30 years	2	1.41 (1.12, 1.79)	0.34	
Pre-pregnancy BMI on average				
<25kg/m^2	3	1.25 (1.08, 1.46)	0.27	0.20
≥25kg/m^2	2	0.81 (0.45, 1.46)	0.05	
Incidence rate				
<8%	3	1.03 (0.60, 1.79)	0.01	0.98
≥8%	2	1.03 (0.97 1.09)	0.26	
Timing of diet assessment				
Pre-pregnancy	2	0.95 (0.36, 2.52)	0.003	0.91
Peri- or during-pregnancy	3	1.03 (0.98, 1.09)	0.50	
Adjusted for parity				
Yes	2	1.21 (0.83, 1.76)	0.006	0.50
No	3	0.96 (0.65, 1.43)	0.08	

BMI, body mass index; CI, confidence interval; NA, not applicable; GDM, gestational diabetes mellitus.

[a] As the study of Goshtasebi et al. (2018) analyzed the same population with that of Lamyian et al. (2017) but focused on differently prepared potato foods, we selected the former one to be pooled in the overall analysis.

[b] West region included countries such as the United States and Iceland; East region included countries such as China and Iran.