Appendix 1: Study protocol for systematic review and dose-response meta-analysis to evaluate dose-response relationships between blood glucose level and pancreatic cancer risk [posted as supplied by author]

Objective

To clarify the association between prediabetes and pancreatic cancer, and to identify potential linear and nonlinear dose-response relationships between blood glucose level and pancreatic cancer risk.

Inclusion criteria

Study type

Studies which prospectively evaluated the association between blood glucose and pancreatic cancer are eligible for meta-analysis. Retrospective and cross-sectional studies are not eligible.

Participants

Eligible studies should have included participants older than 18 years.

Outcome measures

- Eligible studies should have reported the relative risk (RR) of pancreatic cancer, such as hazard ratios or odds ratios.
- Eligible studies should have reported the numbers of participants and pancreatic cancer patients in each blood glucose level categories, or provided information that enables the calculation of those numbers.

Publication type

- Full-length articles or abstracts in peer-reviewed journals will be eligible.
- No language restrictions will be applied.

Data extraction

- Two investigators (Wei-Chih Liao and Yu-Kang Tu) will independently review full manuscripts of eligible studies to extract information into an electronic database, including author, publication year, country where the study was conducted, study design, sample size, duration of follow-up, methods of blood glucose level measurement/categorization and outcome ascertainment, number and characteristics of cases, RRs and 95% confidence intervals (CIs), and adjusted covariates.
- When relevant information is unclear in the report, or when doubt exists

for duplicate publications, the original authors will be contacted for clarifications.

- Disagreement between the two investigators will be resolved by joint review of the manuscript to reach consensus.

Quality assessment

- Study quality will be assessed independently by two investigators (Wei-Chih Liao and Yu-Kang Tu) using the Newcastle-Ottawa scale[1].
- Disagreements between the two investigators will be resolved by discussion to reach consensus.

Data synthesis and analysis

All data from each eligible study will be extracted and entered into a standardized spreadsheet software (Microsoft Excel 2007; Microsoft Corp, Redmond, WA, USA).

The analyses will be performed using Stata 12 (StataCorp, Texas, USA). All tests of statistical significance are two-sided with the statistical significance level set at 5%.

The outcome to be summarized is the relative risk (RR) of pancreatic cancer, using random-effects meta-analysis models to account for heterogeneity among studies. If only separate RRs for men and women are available in the original report, gender-specific RRs are pooled using fixed-effect models for subsequent meta-analysis when feasible. Fasting blood glucose level will be used as the exposure.[2] For studies which used hemoglobin A1C (HbA1C) or post-load blood glucose level after an oral glucose tolerance test as the exposure, HbA1c and post-load glucose levels will be converted to fasting blood glucose levels by using the following method: the cutoff fasting blood glucose for prediabetes (100 mg/dL) and diabetes (126 mg/dL) were assumed to be equivalent to the cutoffs of HbA1c (5.6% and 6.5%) and post-load blood glucose (140 mg/dL and 200 mg/dL), respectively.[2 3] For closed-ended blood glucose categories, the median glucose level in each category is assigned as the blood glucose level associated with the corresponding RR. For the highest open-ended category, glucose level is assigned as the lower bound plus 1.5 times width of the neighboring category. For the lowest open-ended category, glucose level is assigned as the median of the upper bound and 70, as the lower limit of fasting blood glucose is normally around 70 mg/dL.[4]

The first analysis is to summarize the RRs for the highest vs the lowest category of fasting blood glucose in included studies using traditional

meta-analysis (high vs low meta-analysis). Potential small study bias was evaluated by funnel plots and by Egger's test and Begg's test.[5] Heterogeneity was evaluated by I^2 and Cochran's Q.[6] Second, for dose-response meta-analysis the study-specific linear trends between exposure and outcome will be estimated using the method described by Greenland and Longnecker to accounts for within-study correlation of the RRs to avoid potential bias.[7 8] The estimated linear trends are then pooled using traditional meta-analysis. Last, potential nonlinear dose-response relationship in each study by is assessed using restricted cubic splines with 3 knots in the dose-response regression model,[8 9] and results from each study are then pooled together using random-effects multivariate meta-analysis.[10 11] The linear and nonlinear models are compared using likelihood ratio tests.[9] Gender-specific effects are examined by conducting separate meta-analyses for men and women.
For sensitivity analysis, first repeat the analysis after excluding RRs which have an assigned fasting blood glucose level greater than 126 mg/dL (cutoff for diagnosing diabetes) to exclude reverse causality and assess whether the observed trend could be mainly due to increased risk associated with type 2 diabetes. Second, repeat the analysis after excluding studies that are incorporated using estimated fasting blood glucose levels.

Search strategies

PubMed and Scopus will be searched for studies from database inception using the following complimentary strategies without language restrictions. Bibliographies of included studies and related reviews will be manually searched for additional references.

- **Search 1：PubMed, inception through November 30, 2013**

"pancreatic neoplasms"[MeSH Terms] OR "pancreatic neoplasms"[All Fields] OR "pancreatic cancer"[All Fields]

- **Search 2：PubMed, inception through November 30, 2013**

"pancreatic neoplasms"[MeSH Terms] OR ("pancreatic"[All Fields] AND "neoplasms"[All Fields]) OR "pancreatic neoplasms"[All Fields] OR ("pancreatic"[All Fields] AND "cancer"[All Fields]) OR "pancreatic cancer"[All Fields]) AND ("risk"[MeSH Terms] OR "risk"[All Fields]) AND ("glucose"[MeSH Terms] OR "glucose"[All Fields]

- **Search 3：Scopus, inception through November 30, 2013**

TITLE-ABS-KEY("pancreatic
cancer" AND glucose) AND DOCTYPE(ar OR re) AND SUBJAREA(mult OR a gri OR bioc

ORimmu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal)

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