Supplementary Files

Supplementary methods

All the included studies divided the continuous variables (fasting glucose, fasting insulin, HbA1c, C-peptide and HOMA-IR) into categories and most of them provided risk ratios (if only cases numbers of different categories were provided, we recalculated the risk ratio). The cut-off values were listed in the supplementary excel table.

1) Fasting glucose. 18 studies were finally included which met the criteria (studies didn't provided detailed description for the blood glucose measurement were excluded, because we can't make sure it was fasting glucose or not). For the included 18 studies, 13 studies measured the fasting blood glucose level in a unit of "mg/dl" and 5 studies used "mmol/L". And we made transformations on those data in "mmol/L" with a formula "1 mmol/L=18mg/dl" for fasting blood glucose dose-response analysis. All studies except one (Hakozaki et al, 2013[46]) provided risk ratios on the different categories of fasting glucose level, while the number and cut-off value of categories varied among these included studies. Hakozaki et al[46] only provided the case number of different categories and we recalculated the risk ratio by a fourfold table chi square method (available at http://vassarstats.net/odds2x2.html).

2) Fasting insulin. 10 studies were finally included, and the unit of fasting insulin were different among these studies, such as "uIU/ml, uIU/dl, pmol/L, and mIU/L". And we made transformations on those data "1 pmol/L=6.965mIU/L=6.965uIU/L" for fasting blood insulin dose-response analysis.

3) HOMA-IR. 8 studies were included and 7 provided the category information and cut-off values, while Erarslan et al, 2014[48] only provided the odd ratio for this case-control study. HOMA-IR was calculated according to the formula fasting glucose (mmol/L) × fasting insulin (mIU/L) / 22.5.

4) HbA1c. 8 studies were included and all used "%" as unit of HbA1c. No additional recalculation was made.

5) C-peptide. 9 studies were included. Two reported c-peptide level by the unit "pmol/ml", and five used "ng/ml", and the rest two studies didn't provided the detailed category information. We made transformations on those data "1 pmol/ml=3.02ng/ml" for C-peptide dose-response analysis.

Supplementary Table 1. Characteristics of included studies.

Study	Region	Design	Gender	Age(years)	Cancer types and No. of participants	Study quality	Adjustment for covariates
Yamada et al,1998[17]	Japan	case-control	F/M	34-73	CRC:129 control:258	9	age, sex, BMI, alcohol consumption
Platz et al,1999[18]	USA	nested case-control	F	44-69	CRC:79 control:156 cohort:121700	5	year of birth, month of blood draw, and fasting state
Schoen et al,1999[19]	USA	cohort	F/M	73.9(mean)	CRC:102 cohort:5849	8	age, sex and physical activity
Kaaks et al,2000[20]	USA	nested case-control	F	35-65	CRC:102 control:200 cohort:14275	8	age, menopausal status, day of menstrual cycle (for premenopausal women), and time of last food consumption and smoking status
Palmqvist et al,2003[21]	Sweden	case-control	F/M	30-70	CC:110 RC:58 control:336	9	age, sex, BMI, smoking, IGFBP levels
Saydah et al,2003[22]	USA	case-control	F/M	>18	CC:132 RC41 control:346	8	age, sex, race, time since last meal, and date of blood draw
Khaw et al,2004[23]	UK	cohort	F/M	45-79	CRC:67 cohort:9605	8	sex, BMI, smoking habit
Ma et al,2004[24]	USA	nested case-control	M	40-84	CRC:176 control:294 cohort:14916	7	age, smoking status, fasting status, BMI, alcohol consumption, vigorous exercise, and aspirin assignment
Stattin et al	Norway	nested	M	45(mean)	CC:235	8	leptin by adding it as continuous

al,2004[25]			case-control			RC:143 control:378 cohort:600000		variable to the model.
Lin et al,2005[27]	USA	cohort	F	≥45		CRC:168 cohort:27110	7	age, random treatment assignment, BMI, family history of CRC and colon polyps, physical activity, smoking status, red meat intake, alcohol consumption, total energy intake, multivitamin use, menopausal status, and baseline postmenopausal hormone use
Jee et al,2005[26]	Korea	cohort	F/M	30-95		CRC:3352 cohort:829770men 468615women	8	age, age squared, amount of smoking, and alcohol use
Wei et al,2005[28]	USA	nested case-control	F	30-55		CRC:182 control:350 cohort:32826	7	BMI, physical activity, pack-years smoked, and alcohol intake as continuous variables, family history of CRC, aspirin use, history of screening, menopausal status, and use of postmenopausal hormones
Chung et al,2006[29]	Korea	case-control	F/M	CRC58.4,control58.7		CRC:105 control:105	8	age, sex, BMI, TG, cholesterol
Limburg et al,2006[30]	Finland	nested case-control	M	50-69		CRC:139 control:399 cohort:29133	8	cigarette pack-years, body mass index, protein intake, fat intake, fiber intake, alcohol consumption, caloric intake, history of diabetes mellitus

								and occupational physical activity.
Rapp et al,2006[31]		Austrian	cohort	F/M		CRC:677 cohort:63585men 77228women	8	age, smoking status, occupational group, and BMI
Jenab et al,2007[32]		10 European countries	nested case-control	F/M	36.7-76.9	CRC:1078 control:1078 cohort:520000	8	Age, gender, BMI, physical activity, laboratory analysis and case-control status
Otani et al,2007[33]		Japan	nested case-control	F/M	40-69	CRC:375 control:750 cohort:38373	8	pack-years of smoking, alcohol consumption, BMI, physical exercise, family history of colorectal cancer and following plasma measurements mutually
Stattin et al,2007[50]		Sweden	cohort	F/M	46(mean)	CC:147 RC:87 cohort:64597	8	age, calendar year, smoking
Gunter et al,2008[34]		USA	nested case-control	F	50-79	CRC:438 control:816 cohort:93676	8	age
Rinaldi et al,2008[35]		10 Europen countries[#]	nested case-control	F/M	35-69	CRC:1026 control:1026 cohort: 370000women 150000men	8	gender, age at blood donation, time of the day at blood donation, follow-up time, fasting status and, in women, menopausal status and phase of the menstrual cycle for premenopausal women
Stocks et al,2008[36]		Sweden	nested case-control	F/M	50-70	CRC:306 control:595	8	case-control status, sex, age, smoking status and fasting time

								before blood draw
Stocks et al,2009[37]		Norway, Austria and Sweden	cohort	F/M	44.8(mean)	CC:2434 RC:1345 cohort: 274126men 275818women	9	adjusted for baseline age, BMI, and smoking status
Nakajima et al,2010[38]		Japan	case-control	F/M	CRC:63.7,cotrol:63.5	CRC:115 control:115	8	age, gender, BMI, tumor stage and tumor location
Yamamoto et al,2010[39]		Japan	case-control	F/M	53.8(mean)	CRC:22 control:66	8	BMI, smoking and drinking
Stocks et al,2011[40]		Norway	cohort	F/M	44(mean)	CRC:4695 cohort:578500	8	baseline age, birth year, smoking status, and quintiles of BMI
Wu et al,2011[41]		USA	nested case-control	M	40-75	CRC:499 control:992	9	age, gender, BMI, month of blood donation, smoking status, physical activity, intake of alcohol, methionine, folate, retinol, red and processed meat, calcium intake, family history of CRC, fasting status
Chen et al,2012[42]		China	case-control	M	early cancer62.1 advanced cancer61.8 control58.3	CRC:165 control:102	7	age, BMI, WHR, SBP, TG, total adiponectin, fasting insulin, HOMA-IR, HMW adiponectin, lifestyle characteristics, medications, family history of CRC and diabetes
Dankner et al,2012[43]		Four region*	cohort	F/M	51.8(mean)	CRC:44 cohort:1695	9	age, sex, and ethnicity
Kabat et al		UK	nested	F	50-79	CRC:81	8	age, BMI, alcohol intake, physical

Author	Country	Study type	Sex	Age	Sample	Score	Adjustments
al,2012[49]		case-control			control:4821 cohort:4902		activity, family history of colorectal cancer, ethnicity, and participation in the OS or treatment arm of each clinical trial.
Ollberding et al,2012[44]	USA	nested case-control	F/M	45-75	CRC:1954 control:2587 cohort:215000	8	age, sex, race/ethnicity, history of colorectal polyp, family history of colorectal cancer, BMI, physical activity, processed meat intake, pack-years of smoking, alcohol consumption, and mutual adjustment for IGF-I and IGFBP-3,
Wulaningsih et al,2012[45]	Sweden	cohort	F/M	43.84(mean)	CC:2472 RC:1510 cohort:540309	8	glucose, TC and TG levels, age, gender, SES, and fasting status
Hakozaki et al,2013[46]	Japan	case-control	F/M	48(mean)	CRC:29 control:440	7	age, gender, cholesterol, triglyceride, uric acid
Parekh et al,2013[47]	USA	cohort	F/M	66.8(mean)	CRC:136 cohort:4615	8	age, sex, alcohol, smoking, BMI, smoking status
Erarslan et al,2014[48]	Turkey	case-control	F/M	CRC58,control52.9	CRC:21 control:30	9	age, BMI, VFA, serum IGF-1, fasting insulin and glucose
Shin et al,2014[51]	Korea	cohort	F/M	42(mean)	CRC:320 cohort:175677	9	age, sex, body mass index, smoking, alcohol drinking, and regular exercise

Nr: not reported;

[#]: Denmark, France, Germany, Greece, Italy, Norway, Spain, Sweden, the Netherlands, and the United Kingdom;

[*]: European-American, North African, Yemenite, and Other Middle Eastern.

Study quality was judged on the basis of the Newcastle-Ottawa Scale (1-9 stars)

Supplementary Table 2. Quality assessment of case-control studies.

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Quality
Yamada et al,1998	a	a	a	a	ab	a	a	a	9
Platz et al,1999	c	b	b	b	ab	a	a	a	5
Kaaks et al,2000	c	a	a	a	ab	a	a	a	8
Palmqvist et al,2003	a	a	a	a	ab	a	a	a	9
Saydah et al,2003	b	a	a	a	ab	a	a	a	8
Ma et al,2004	a	b	b	a	ab	a	a	a	7
Stattin et al,2004	b	a	a	a	ab	a	a	a	8
Wei et al,2005	a	b	b	a	ab	a	a	a	7
Chung et al,2006	a	a	b	a	ab	a	a	a	8
Limburg et al,2006	b	a	a	a	ab	a	a	a	8
Jenab et al,2007	b	a	a	a	ab	a	a	a	8
Otani et al,2007	b	a	a	a	ab	a	a	a	8
Gunter et al,2008	b	a	a	a	ab	a	a	a	8
Rinaldi et al,2008	b	a	a	a	ab	a	a	a	8
Stocks et al,2008	b	a	a	a	ab	a	a	a	8
Nakajima et al,2010	a	a	b	a	ab	a	a	a	8
Yamamoto et al,2010	a	a	b	a	ab	a	a	a	8
Wu et al,2011	a	a	a	a	ab	a	a	a	9
Chen et al,2012	a	a	b	a	a	a	a	a	7
Kabat et al,2012	a	a	a	b	ab	a	a	a	8
Ollberding et al,2012	b	a	a	a	ab	a	a	a	8

Hakozaki et al,2013	c	a	b	a	ab	a	a	a	7
Erarslan et al,2014	a	a	a	a	ab	a	a	a	9

Q1: Is the case definition adequate?

a) yes, with independent validation □   b) yes, eg record linkage or based on self-reports   c) no description

Q2: Representativeness of the cases

a) consecutive or obviously representative series of cases   □b) potential for selection biases or not stated

Q3: Selection of Controls

a) community controls □   b) hospital controls   c) no description

Q4: Definition of Controls

a) no history of disease (endpoint) □   b) no description of source

Q5: Comparability of cases and controls on the basis of the design or analysis

a) study controls for age   □   b) study controls for any additional factor

Q6: Ascertainment of exposure

a) secure record   □   b) structured interview where blind to case/control status □

c) interview not blinded to case/control status   d) written self-report or medical record only

e) no description

Q7: Same method of ascertainment for cases and controls

a) yes □b) no

Q8: Non-Response rate

a) same rate for both groups □ b) non respondents described   c) rate different and no designation

Supplementary Table 3. Quality assessment of cohort studies.

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Quality
Schoen et al,1999	b	a	a	a	a	b	a	b	8

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Score
Khaw et al,2004	a	a	a	a	a	b	a	b	8
Lin et al,2005	a	a	a	a	ab	d	a	d	7
Jee et al,2005	a	a	a	a	a	a	a	b	8
Rapp et al,2006	a	a	a	a	a	b	a	b	8
Stattin et al,2007	a	a	a	a	ab	d	a	b	8
Stocks et al,2009	a	a	a	a	ab	b	a	b	9
Stocks et al,2011	a	a	a	a	a	b	a	b	8
Dankner et al,2012	a	a	a	a	ab	b	a	b	9
Wulaningsih et al,2012	a	a	a	a	a	b	a	b	8
Parekh et al,2013	a	a	a	a	a	b	a	b	8
Shin et al,2014	a	a	a	a	ab	b	a	b	9

Q1: Representativeness of the exposed cohort

a) truly representative of the average population in the community ☐ b) somewhat representative of the average population in the community

c) selected group of users   d) no description of the derivation of the cohort

Q2:Selection of the non exposed cohort

a) drawn from the same community as the exposed cohort ☐b) drawn from a different source

c) no description of the derivation of the non-exposed cohort

Q3: Ascertainment of exposure

a) secure record ☐   b) structured interview ☐

c) written self-report   d) no description

Q4: Demonstration that outcome of interest was not present at start of study

a) yes ☐   b) no

Q5: Comparability of cohorts on the basis of the design or analysis

a) study controls for age   b) study controls for any additional factor Outcome

Q6: Assessment of outcome

a) independent blind assessment ☐ b) record linkage ☐

c) self-report   d) no description

Q7: Was follow-up long enough for outcomes to occur

a) yes ☐   b) no

Q8: Adequacy of follow up of cohorts

a) complete follow up - all subjects accounted for ☐

b) subjects lost to follow up unlikely to introduce bias - small number lost > 70 % follow up, or description provided of those lost

c) follow up rate < 70% and no description of those lost

d) no statement

Supplementary Table 4: PRISMA 2009 Checklist and PRISMA Flow diagram

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1-2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8

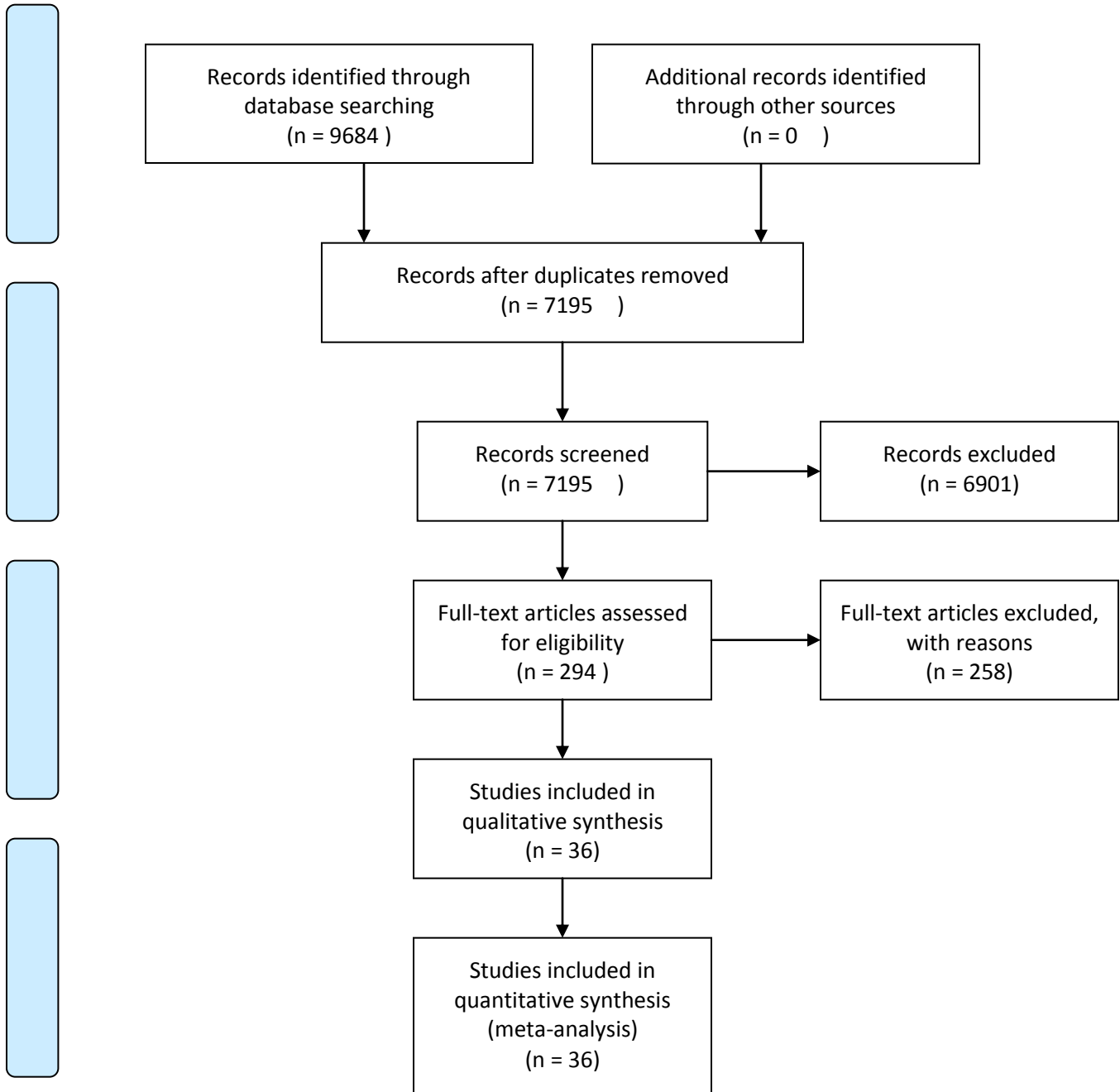| Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			**RESULTS**
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-13
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency	9-13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9-13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17-18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18-19

For more information, visit: **www.prisma-statement.org**.

Flow Diagram

Records identified through
database searching
(n = 9684)

Additional records identified
through other sources
(n = 0   )

Records after duplicates removed
(n = 7195   )

Records screened
(n = 7195   )

Records excluded
(n = 6901)

Full-text articles assessed
for eligibility
(n = 294)

Full-text articles excluded,
with reasons
(n = 258)

Studies included in
qualitative synthesis
(n = 36)

Studies included in
quantitative synthesis
(meta-analysis)
(n = 36)

For more information, visit www.prisma-statement.org.