Online supplementary material

Table S1: STROBE Statement—checklist of items that should be included

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5

		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*NA*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	5-6
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	NA

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	5-6

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	8-9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8-9
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*8-9*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*8-9*
		Cross-sectional study—Report numbers of outcome events or summary measures	*8-9*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Fig 3-4
		(*b*) Report category boundaries when continuous variables were categorized	NA

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Table S2 : The cohorts studies assessed by NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

	Author Year	**Cheng 2014**	**Wahlqvist2012**	**Hsu 2011**	**Kuan 2017**	**Ng** 2014	**Heneka** 2015	**Brakedal** 2017	**Orkaby 2017**	**Wang** 2017	**Weinstein 2019**	**Koo 2017**	**Huang 2014**	**Tseng 2019**
Selection	Representativeness of the exposed cohort	+	+	+	+	-	+	+	+	+	+	+	+	+
	Selection of the non exposed cohort	+	+	+	+	-	+	+	+	+	+	+	+	+
	Ascertainment of exposure(secure record or structured interview)	+	+	+	+	+	+	+	+	+	+	+	+	+
	Demonstration that outcome of interest was not present at start of study	+	+	+	+	-	+	+	+	+	+	+	+	+
Comparability	Study controls for the most important factor	-	-	-	-	+	-	-	+	+	+	-	-	-
	study controls for any additional factor (This criteria could be modified to indicate specific control for a second important factor)	+	+	+	+	+	+	+	+	+	+	+	+	+

Outcome	Assessment of outcome	+	+	+	+	+	+	+	+	+	+	+	+	+
	Was follow-up long enough for outcomes to occur	+	+	+	+	+	+	+	+	+	+	-	+	+
	Adequacy of follow up of cohorts	-	-	-	-	-	-	-	-	-	-	-	-	-
	Study quality score	**7**	**7**	**7**	**7**	**5**	**7**	**7**	**8**	**8**	**8**	**6**	**7**	**7**

Table S3 : Three cross-sectional studies evaluated by Agency for Healthcare Research and Quality methodology checklist

Author Year	2019 Porter	2016 Liccini	2015 Yokoyama
1) Define the source of information (survey, record review)	+	+	+
2) List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications	+	+	+
3) Indicate time period used for identifying patients	+	+	+
4) Indicate whether or not subjects were consecutive if not population-based	+	-	-
5) Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants	-	-	-
6) Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements)	+	-	-
7) Explain any patient exclusions from analysis	+	+	-
8) Describe how confounding was assessed and/or controlled.	+	+	+
9) If applicable, explain how missing data were handled in the analysis	-	-	-
10) Summarize patient response rates and completeness of data collection	-	-	-
11) Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained	-	-	-
Study quality score	7	5	4

Table S4 : The case-control studies assessed by NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

	Author Year	**Imfeld 2012**	**Bohlken 2018**	**Moore 2013**

Selection	Is the case definition adequate	+	+	+
	Representativeness of the cases	+	+	+
	Selection of Controls	+	+	+
	Definition of Controls	+	+	+
Comparability	Study controls for the most important factor	-	+	+
	Study controls for any additional factor	+	+	+
Exposure	Ascertainment of exposure	+	+	+
	Same method of ascertainment for cases and controls	+	+	+
	Non-Response rate	-	-	-
	Study quality score	**7**	**8**	**8**

Table S5 The confunding factors adjusted for in each study

Study	Confunding Variables adjusted for
Porter 2019[22]	Age, GFR， education, VitB 12 and PLP
Cheng 2014[13]	Age, gender, hypertension, hyperlipidemia, and cerebrovascular disease.
Wahlqvist 2012[11]	age, gender, locality, level of care, comorbidity index, monthly income
Hsu 2011[12]	Age, gender, type of smoke and CCI score
Kuan 2017[7]	Age, gender, CCI score; Adapted Diabetes, CSI, comorbidities of HTN, CKD, hyperlipidemia, heart failure, arrhythmia, stroke, head injury, CAD, ADD other than Met, anti-HTN drug, and statin.
Ng 2014[16]	Age, gender, education, depressive symptoms, HTN, CAD, stroke, CKD, other medical co-morbidities , other ADD, APOE-4 carrier status， FBG, BMI, duration of follow up and duration of diabetes
Imfeld 2012[23]	Age, gender, GP, ADD, smoking, BMI, HTN, dyslipidemia, and use of ACEI and statins
Heneka 2015 [17]	Age, gender, CAD comorbidities
Moore 2013[24]	Age, gender, history of depression, education, VitB12

Brakedal 2017[8]	Age, gender
Orkaby 2017[18]	race, gender, BMI, HbA1c, region, eGFR and comorbidities of CAD, HF, AF, HTN, hyperlipidemia, peripheral artery disease, cerebrovascular disease, eye disease, cancer, arthritis, major psychiatric disease and number of drug classes
Liccini 2016[21]	age, gender, education and HbA1c
Yokoyama 2015[20]	Age, gender, BMI, current smoker, duration of diabetes, hypertension, dyslipidemia, and history of CAD and stroke
Wang 2017[19]	Age, ethnicity, CCI, BMI, HbA1c, statin use and propensity, scores of metformin use
Weinstein 2019[9]	Age, gender, education, interval between examination, physical activity, HTN, CVD, stroke, lipid, smoking, depression, and BMI
Koo 2017[10]	Age, gender, education, dementia medication
Bohlken 2018[25]	HbA1c, index date, DM duration, co-diagnoses and co-therapies
Huang 2014[14]	age, gender, comorbidities (HTN, hyperlipidemia, stroke, coronary artery disease, arrhythmia, heart failure and depression), geographic area and urbanization status

Tseng 2019[15]	Propensity score matched including age, gender, occupation, living region, major comorbidities and other medications commonly used in DM patients

Abbreviations: GFR, Glomerular Filtration Rate; SU, sulfonylurea;CCI, Charlson comorbidity index; CSI, Complications Severity Index; HTN, hypertension; CKD, chronic kidney disease; CAD coronary artery disease; ADD, Antidiabetes drug; FBG fasting blood glucose，BMI body mass index；ACE-I angiotensin-converting enzyme inhibitors

Table S6：Subgroup Analysis to Examine Sources of Heterogeneity Observed in Summary Estimate

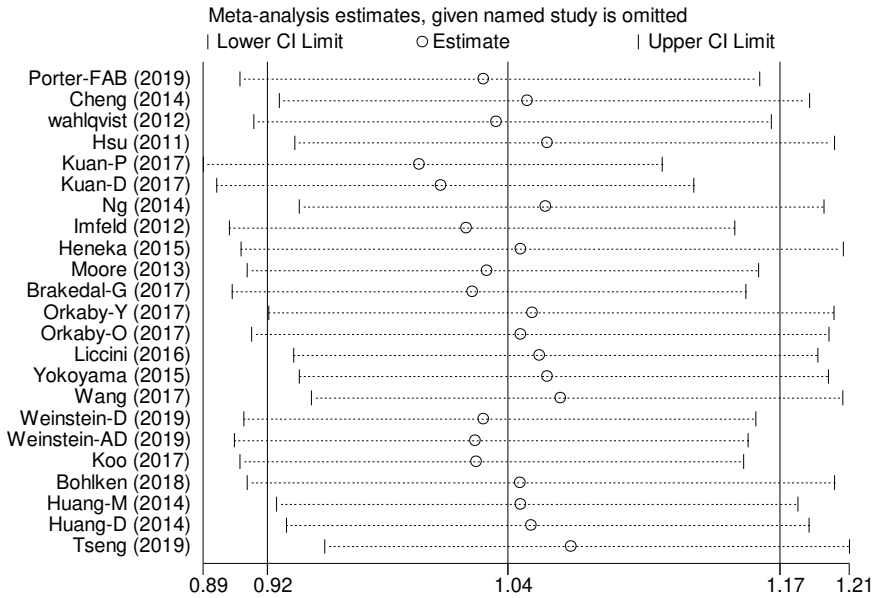
Subgroup analysis	No. of studies	Total no. of subjects	Adjusted OR	95% CI	Tests of heterogeneity		Heterogeneity between subgroups (P)
					P	I^2 （%）	
subtypes of ND							<0.001
PD	3	115805	1.66	1.14-2.42	0.04	68.5	
AD	3	183510	0.90	0.47-1.73	0.06	65.6	
Dementia	17		0.96	0.85-1.09	<0.001	83.1	

Race							0.174
Asian	11	100541	0.97	0.69-1.36	<0.001	90.3	
Caucasian	12	198774	1.04	0.93-1.15	<0.001	71.1	
Study design							0.716
Cohort	17	264670	1.04	0.89-1.21	<0.001	87.1	
Cross-sectional	3	3825	0.77	0.41-1.46	0.01	79.9	
Case-control	3	30820	1.33	0.82-2.16	0.01	77.2	
Study quality assessment							
Low quality	5	4947	0.86	0.5-1.48	0.001	79.1	0.894
High quality	18	294368	1.07	0.94-1.21	<0.001	86.3	

Table S7: Effect of study variables by meta-regression

		Incidence of ND		
		Exp(b)	95% CI	p
Race	Caucasian	1.066	0.731-1.57	0.727
	Asian	0.910	0.648-1.277	0.568
Study design	case-control	1.007	0.353-2.869	0.989
	cohort	0.970	0.354-2.656	0.951
	Cross-sectional	0.979	0.363-2.641	0.965
Subtypes of ND	AD	0.688	0.165-2.866	0.591
	Dementia	0.551	0.245-1.240	0.141
	PD	1.695	0.764-3.757	0.182

FigS1: Sensitivity Analysis plot



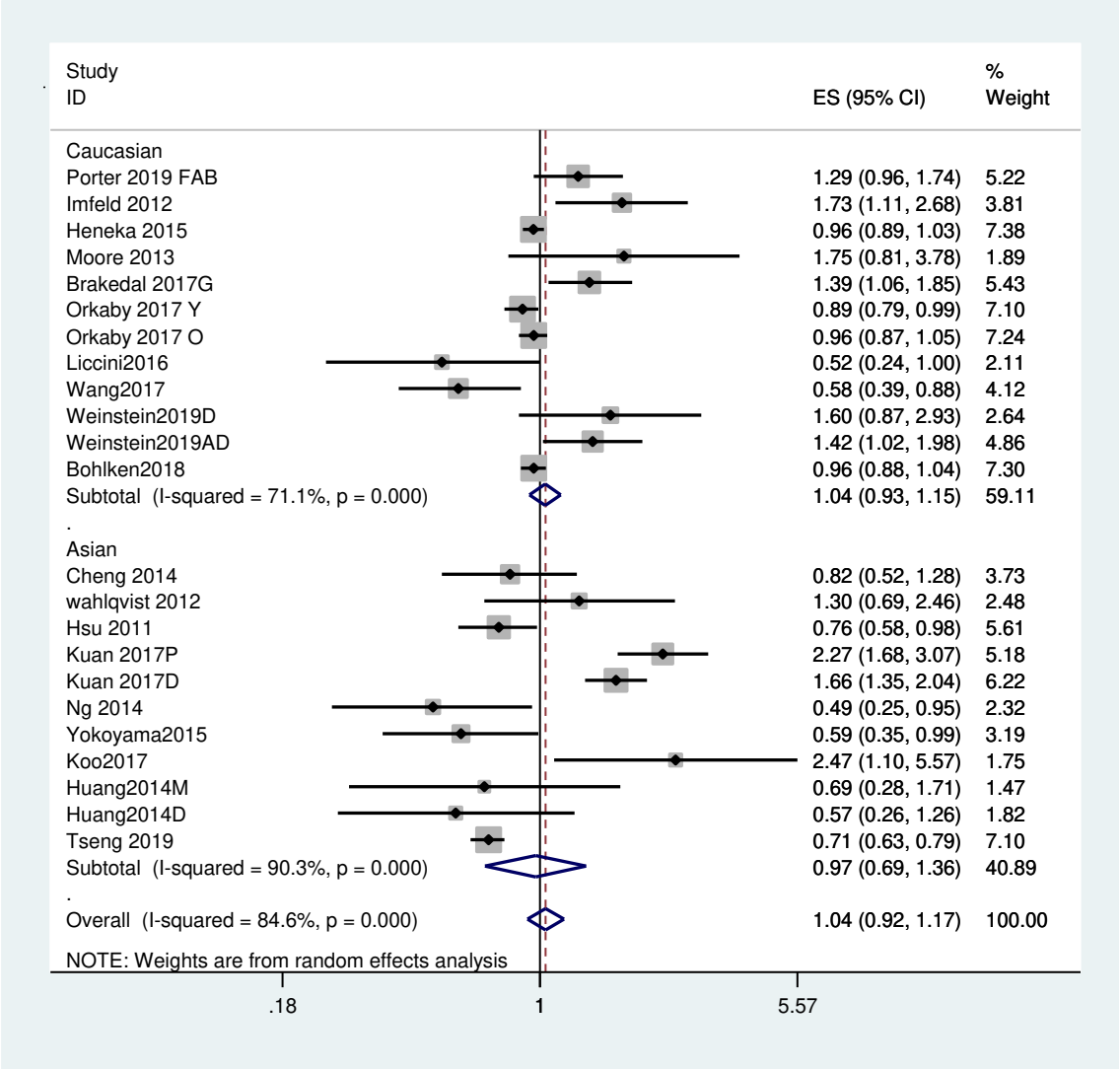


Fig S2 Forest Plot for Subgroup analysis based on different race

Fig S3 Forest Plot for Subgroup analysis based on different study design