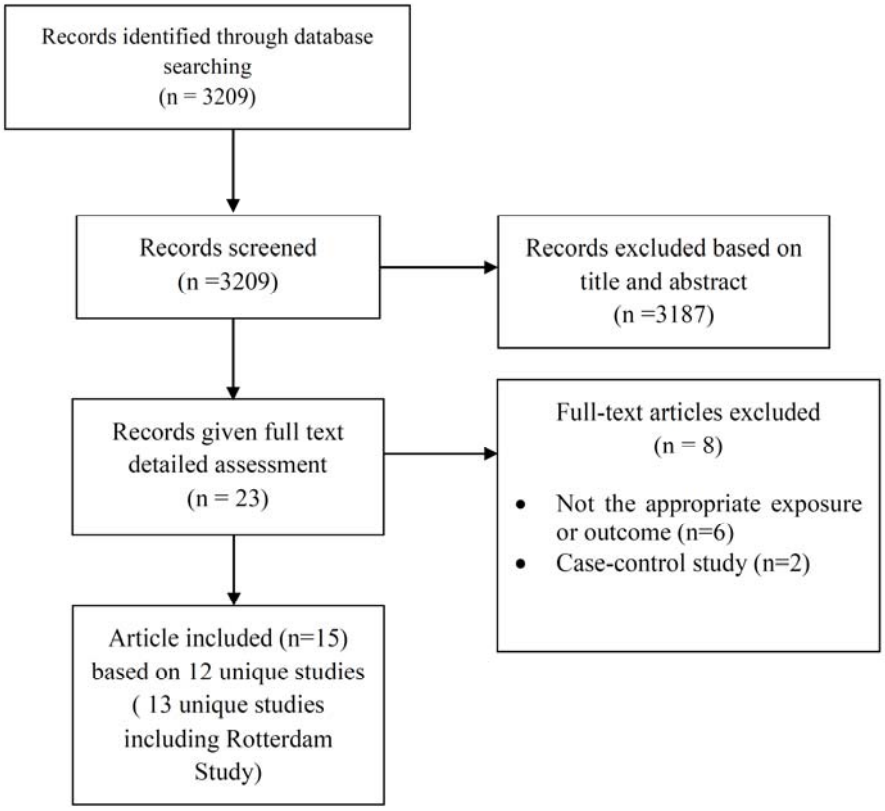
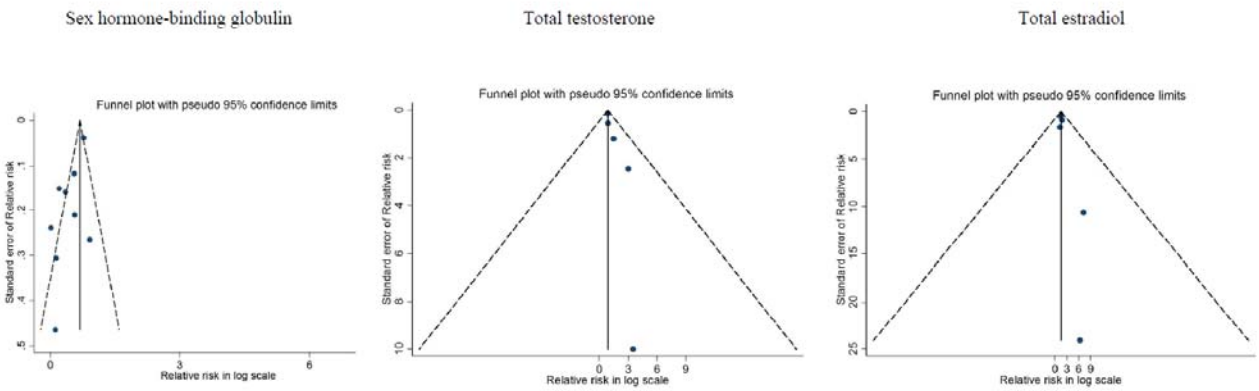
SUPPLEMENTARY DATA

Supplementary Figure S1. Flowchart of studies investigating the association between endogenous sex hormones and the risk of type 2 diabetes.



SUPPLEMENTARY DATA

Supplementary Figure S2. Assessment of small study effects by funnel plots and Egger's test in prospective studies of of sex-hormone binding globulin, sex hormones and type 2 diabetes.



The dotted lines show 95% confidence intervals around the overall summary estimate calculated using a fixed effect model; *p*-values for bias calculated using Egger's test was 0.014, 0.08 and 0.18 for sex hormone-binding globulin, total testosterone and total estradiol, respectively.

SUPPLEMENTARY DATA

Supplementary Table S1. Sensitivity analysis of sex and the risk of type 2 diabetes postmenopausal women, the Rotterdam Study.

	Sex hormone-binding globulin[a]	Total Testosterone[a]	Estradiol[b]	Free androgen index[a]
Multivariable model	**0.66 (0.51-0.86)**	0.93 (0.76-1.14)	**1.002 (1.001-1.004)**	1.15 (0.85-1.54)
Multivariable model + waist circumference	**0.69 (0.53-0.90)**	0.96 (0.78-1.19)	**1.003 (1.001-1.005)**	1.11 (0.92-1.33)
Multivariable model + HDL + TG + LDL	**0.72 (0.55-0.95)**	0.94 (0.76-1.16)	**1.003 (1.001-1.004)**	1.07 (0.89-1.29)
Multivariable model + serum thyroid stimulating hormone	**0.66 (0.51-0.87)**	0.89 (0.73-1.09)	**1.002 (1.001-1.004)**	1.11 (0.93-1.33)
Multivariable model + physical activity	**0.66 (0.50-0.86)**	0.89 (0.73-1.09)	**1.003 (1.001-1.004)**	1.12 (0.94-1.34)
Multivariable model + menopause type (surgical vs. natural)	**0.65 (0.50-0.85)**	0.89 (0.72-1.08)	**1.003 (1.001-1.004)**	1.12 (0.94-1.34)
Multivariable model + number of pregnancies of at least 6 months	**0.65 (0.51-0.85)**	0.94 (0.76-1.15)	**1.003 (1.001-1.004)**	1.12 (0.94-1.34)
Multivariable model excluding the first 3 years of follow-up	**0.68 (0.51-0.91)**	0.98 (0.79-1.23)	**1.003 (1.001 -1.005)**	1.13 (0.93-1.37)
BMI (kg/m^2)[c]				
<25	**0.50 (0.28-0.91)**[d]	0.90 (0.56-1.45)[d]	**1.003 (1.001-1.006)**[d]	1.18 (0.78-1.78)[d]
25-29.9	0.80 (0.54-1.18)	1.20 (0.88-1.62)	1.003 (1.00-1.006)	1.22 (0.94-1.58)
≥30	0.76 (0.48-1.22)	0.86 (0.59-1.24)	1.001 (1.00-1.005)	0.99 (0.72-1.36)
Time since menopause[c]				
<15	0.84 (0.47-1.50)[d]	1.26 (0.84-1.89)[e]	**1.004 (1.001-1.007)**[d]	1.22 (0.86-1.73)[k]
15-25	0.78 (0.51-1.19)	1.01 (0.73-1.40)	1.002 (0.998 -1.006)	1.09 (0.83-1.44)
>25	**0.46 (0.28-0.75)**	0.78 (0.55-1.10)	1.003 (0.996 -1.01)	1.08 (0.79-1.48)

Multivariable model adjusted for variables in model 3 of Table 2.
[a] Values are + 1 log increase
[b] Values are per 1 unit increase
[c] Results are adjusted for variables in model 3 of Table 2
[d] P-interaction >0.05
[e] P-interaction=0.019
[k] P-interaction=0.03

SUPPLEMENTARY DATA

Supplementary Table S2. Characteristics of the included studies that assessed the association of sex hormones with the risk of type 2 diabetes

Lead Author, Publication Date	Name of study or source of participants	Location	Year of baseline survey	Baseline age range/ average age (years)	Study design	Follow up years	Total participants	No. of study events	Menopausal Status	Covariates adjusted for	Study quality*
Oh 2002	RBS	USA	1984-1987	72.4 ± 6.14	Case-cohort	8	233	17	Postmenopausal	Age, BMI, systolic blood pressure,	7
Chen BH et al.2012 Ding 2007 and 2009	WHI-OS	USA	1994-1998	61.1 ± 5.2	Case-cohort	5.9 (median)	1928	642	Postmenopausal	Age, race/ethnicity, clinical center, time of blood flow, duration of follow-up, postmenopausal hormone therapy, physical activity, smoking status, alcohol intake, history of hypertension, family history of diabetes, body mass index, C-reactive protein, HOMA-IR, testosterone, LDL, HDL-cholesterol, glycated haemoglobin.	8

SUPPLEMENTARY DATA

Lead Author, Publication Date	Name of study or source of participants	Location	Year of baseline survey	Baseline age range/ average age (years)	Study design	Follow up years	Total participants	No. of study events	Menopausal Status	Covariates adjusted for	Study quality*
Kalyani 2009	MESA	USA	2000-20002	65.2 ± 9.0	Prospective	6	1612	116	Postmenopausal	Age, race/ethnicity, education, income, family history of diabetes, examination site, BMI, HOMA-IR, LDL, HDL, triglycerides, use of lipid-lowering medications, systolic blood pressure, antihypertensive medication, total daily caloric intake, physical activity, smoking, IL-6, CRP, age at menopause, years since menopause, type of menopause, age at first live birth, five or more live births, and past use of hormone replacement therapy r oral contraceptive pills.	9
Onat 2010	TARFS	Turkey		48.4 ± 11.7	Case-cohort	9	1067	202	Pre- and post-menopausal	Age, BMI, C-reactive protein, HDL-cholesterol, lipid lowering drugs and Apolipoprotein A-1	7
Haffner 1993	SAHS	USA	1979-1982	25-64	Case-cohort	8	109	38	Pre- and post-menopausal	Fasting glucose and insulin	7
Soriguer 2011	PCS	Italy	1995-1997	36 ± 23	Case-cohort	11	691	106*	Pre- and post-menopausal	Age, body mass index and waist circumference	8

SUPPLEMENTARY DATA

Lead Author, Publication Date	Name of study or source of participants	Location	Year of baseline survey	Baseline age range/ average age (years)	Study design	Follow up years	Total participants	No. of study events	Menopausal Status	Covariates adjusted for	Study quality*
Gambineri 2012	NA	Italy	1978-1999	23.4 ± 6.3	Prospective	16.9	255	42	Pre-menopausal	Age, BMI, fasting glucose, waist to hip ratio, systolic blood pressure, diastolic blood pressure, fasting insulin, HbA1C, total cholesterol, HDL-cholesterol, triglycerides, luteinizing hormone, follicle-stimulating hormone, estradiol, testosterone, SHBG	8
Lindstedt G et al. 1991	NA	Sweden	1968-1969	38-60	Prospective	12	1462	43	Pre and postmenopausal	NA	7
Boyd-Woschinko 2007	NA	USA		36-43	Case-cohort	8	119	10	Pre-menopausal	NA	5
Okubo M et al. 1999	Medical survey	Hawaii and USA	1992-1993	65.4 ± 0.5	Prospective	3	280	23	Postmenopausal	Age, body mass index and waist to hip ratio	6
Fenske B et al. 2015	Study of Health in Pomerania	Germany	1997-2001	48.8 ± 16.2	Prospective	5	1925	202*	Pre and postmenopausal	Age, waist circumference, physical inactivity and alcohol consumption.	8

SUPPLEMENTARY DATA

Lead Author, Publication Date	Name of study or source of participants	Location	Year of baseline survey	Baseline age range/ average age (years)	Study design	Follow up years	Total participants	No. of study events	Menopausal Status	Covariates adjusted for	Study quality*
Hu J et al. 2015	EIMDS	China	2008	60 ± 11.1	Prospective, nested case-control	5	174	87	Postmenopausal	BMI, systolic blood pressure, diastolic blood pressure, current smoking, alcohol use, hypertension, exercise frequency, family history of T2D, fasting plasma glucose, total cholesterol, high-density lipoprotein cholesterol and low density lipoprotein cholesterol.	8
Mather 2015	DPP	USA	1997	50.9 ± 7.9	Prospective	3	1930	ND	Pre and postmenopausal	Age, ethnicity, smoking, alcohol consumption, leisure activity, waist circumference, fasting insulin and insulinogenic index	7
Total							14,902	1912			

BMI, Body mass index; DPP, Diabetes Prevention Program; EIMDS, The Environment, Inflammation and Metabolic Diseases Study; MESA, Multi-Ethnic Study of Atherosclerosis; ND, not determined; PCS, Pizarra Cohort Study; RBS, Rancho Bernardo Study; SAHS, San Antonio Heart Study; TARFS, Turkish Adult Risk Factor Study; WHS, Women Health's Study

*approximation

SUPPLEMENTARY DATA

Supplementary Table S3. Assays used to assess sex hormones and sex hormone binding globulin across the studies included in the systematic review

Author, year of publication	Estradiol	Testosterone	Sex hormone binding globuline
Oh 2002	Radioimmunoassay; Bioavailable estradiol was determined using a modification of the ammonium-sulfate precipitation method of Tremblay and Dube.	Radioimmunoassay; Bioavailable testosterone was determined using a modification of the ammonium-sulfate precipitation method of Tremblay and Dube.	NA
Chen BH et al.2012 Ding 2007 and 2009	Chemiluminescent immunoassays (Elecsys Autoanalyzer 2010; Roche Diagnostics, Indianapolis, IN, USA. Free oestradiol and free testosterone were calculated via the Sodergard method.	Chemiluminescent immunoassays (Elecsys Autoanalyzer 2010; Roche Diagnostics, Indianapolis, IN, USA. Free oestradiol and free testosterone were calculated via the Sodergard method.	Chemiluminescent immunoassays (Elecsys Autoanalyzer 2010; Roche Diagnostics, Indianapolis, IN, USA
Kalyani 2009	An ultrasensitive RIA kit from Diagnostic Systems Laboratories (Webster, TX).	Measured directly using RIA kits. Concentrations of free T, SHBG-bound T, and albumin-bound T were calculated according to the method of So¨ dergård et al., allowing for determination of bioavailable T as the sum of SHBG-bound T and albumin-bound T.	Chemiluminescent enzyme immunometric assay using Immulite kits obtained from Diagnostic Products Corp
Onat 2010	NA	NA	Chemiluminescent immunometric method using Roche kits and Elecsys 1010 immunautoanalyzer (Roche Diagnostics, Mannheim, Germany).
Haffner 1993	NA	NA	Immunoradiometric assay technique (Diagnostic Products Corp, Los Angelos, CA)
Soriguer 2011	NA	Enzyme immunoassay (ELISA) (DRG Instruments GMBH, Bioavailable testosterone (nM) (bioT) was calculated according to Morris et al. Marburg, Germany)	Enzyme immunoassay (ELISA) (DRG Instruments GMBH, Marburg, Germany)

SUPPLEMENTARY DATA

Gambineri 2012	NA	NA	Not defined
Lindstedt G et al. 1991			Immunoradiometric assay technique
Boyd-Woschinko 2007	NA	NA	Radioimmunoassay
Okubo M et al. 1999	NA	NA	IRMA kit (Orion Diagnostica, Finland).
Fenske B et al. 2015	NA	Liquid chromatography-tandem mass spectrometry (LC-MS). Free testosterone (fT) was calculated as a relation between measured TT and SHBG levels for a standard average albumin concentration of 4.3 g/dL.	Advia Centaur (Siemens, Eschborn, Germany)

NA, not available.

SUPPLEMENTARY DATA

Supplementary Table S4. Pooled relative risks for type 2 diabetes by characteristic of study participants.

Subgroups by Study Characteristics	**Menopause status**	**Number of studies**	**Number of participants**	**Number of type 2 diabetes cases**	**Relative Risk (95% CI)**	***P*-value for heterogeneity** [a]
	Association between sex hormone binding globulin and risk of type 2 diabetes					
Menopause status	Premenopause	1	119	10	0.12 (0.01, 1.22)	0.91
	Pre- and postmenopause	3	3101	442	0.41 (0.13, 1.28)	
	Postmenopause	5	7056	1271	0.45 (0.28, 0.72)	
Number of participants	<1000	4	627	177	0.20 (0.04, 0.87)	0.39
	≥1000	5	9649	1546	0.44 (0.30, 0.66)	
Location	Europe	4	6334	830	0.64 (0.47, 0.88)	0.08
	America	4	3768	806	0.24 (0.09, 0.68)	
	Asia	1	174	87	0.14(0.10, 0.74)	
	Association between total testosterone and risk of type 2 diabetes					
Menopause status	Pre- and postmenopause	1	1925	202	0.90 (0.41, 1.98)	0.46
	Postmenopause	4	5452	1130	1.58 (0.78, 3.20)	
Number of participants	<1000	4	627	177	1.77 (0.79, 3.94)	0.44
	≥1000	5	9649	1546	1.19 (0.62, 2.29)	
Location	Europe	2	5042	586	0.88 (0.68, 1.14)	0.02
	America	2	2161	656	2.08 (1.05, 4.15)	
	Asia	1	174	87	3.51 (0.62, 23.10)	

[a] P-value for heterogeneity was evaluated using random effects meta-regression.

SUPPLEMENTARY DATA

Supplementary Appendix S1. Potential confounding variables

Information on current health status, medical history, medication use, smoking behaviour, and socioeconomic status was obtained at baseline for both studies. During the home interview, women were asked a special section of questions pertaining to menopausal status. One set of questions dealt with timing of the last menstrual period, gathering information on whether the respondent had a natural menstrual period within the 12 months, the past 3 months, and the age at last period for women who had no period for at least 3 months. One question addressed period regularity and the number of menstrual cycles. Postmenopausal women were defined women who reported absence of menstrual periods for 12 months. Participants were asked whether they were currently smoking cigarettes, cigars, or pipes. Alcohol intake was assessed in grams of ethanol per day. History of cardiovascular disease was defined as a history of coronary heart diseases (myocardial infarction, revascularization, coronary artery bypass graft surgery or percutaneous coronary intervention) and was verified from the medical records of the general practitioner. Blood pressure was measured in the sitting position at the right upper arm with a random-zero-sphygmomanometer. Physical height (m) and body weight (kg) were measured at baseline with the participants standing without shoes and heavy outer garments. Body mass index (BMI) was calculated as weight divided by height squared (kg/m2). All biochemical parameters were assessed in fasting serum. Thyroid stimulating hormone (TSH) was measured on the Vitros Eci (Ortho Diagnostics). Insulin, glucose, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) and C-reactive protein (CRP) were measured on the COBAS 8000 Modular Analyzer (Roche Diagnostics GmbH). The corresponding interassay coefficients of variations are the following: TSH<13.2%, insulin <8%, glucose <1.4%, lipids <2.1% and CRP <16.9%. Physical activity was assessed with an adapted version of the Zutphen Physical Activity Questionnaire[1]. Every activity mentioned in the questionnaire was attributed a MET-value according to the 2011[2].The questionnaire contained questions on walking, cycling, gardening, diverse sports, hobbies and on housekeeping. Total time spend on physical activity was calculated as the sum of minutes per week for each type of activity.

Supplementary Appendix S5.

Data extraction and quality assessment

Data were extracted by two independent reviewers and a consensus was reached with involvement of a third. A predesigned data abstraction form was used to extract relevant information. This included questions on study size; study design; baseline population; location; age at baseline; duration of follow-up (for cohort studies) and menopausal status. Additionally, in the case of multiple publications, the most up-to-date or comprehensive information was included. Study quality was assessed based on the nine-star Newcastle–Ottawa Scale (NOS)[3] using three pre-defined domains namely: selection of participants (population representativeness), comparability (adjustment for confounders), and ascertainment of outcomes of interest. The NOS assigns a maximum of four points for selection, two points for comparability, and three points for outcome. Nine points on the NOS reflects the highest study quality.

SUPPLEMENTARY DATA

Data synthesis and analysis

For the meta-analysis, we used the risk estimates of the most adjust models reported by each study. To enable a consistent approach for the meta-analysis, we used previously described methods[4] to transform RR estimates for associations between sex hormones with T2D risk which were often differentially reported by each study (for example, per unit change, per one standard deviation change, or comparing quarters or thirds, and other groupings), and therefore, to consistently correspond to comparison of the top third versus the bottom of the baseline distribution by sex hormone levels in each study. Briefly, we transformed the log RR by assuming a normal distribution, with the comparison between extreme thirds being equivalent to 2.18 times the log risk ratio for one standard deviation increases (or equivalently as 2.18/2.54 time the log RR for a comparison of extreme quarters). We calculated standard error of the log RR by using published CIs and standardised them in the same way. Hazard ratios, RRs, and odds ratios were assumed to approximate the same measure of RR.
The inverse variance weighted method was used to combine relative risks to produce a pooled relative risk using random-effects models to allow for between study heterogeneity. Also, additionally we reported the estimates using fixed effect models. Heterogeneity was assessed using the Cochrane χ^2 statistic and the I^2 statistic. Publication bias was evaluated through a funnel plot and Egger's test. Menopause status, location and number of participants were pre-specified as characteristics for assessment of heterogeneity, and was evaluated using stratified analyses and random effects meta-regression for the meta-analysis that included 5 or more studies[5]. All tests were two-tailed and p-values of 0.05 or less were considered significant. STATA release 12 (Stata Corp, College Station, Texas) was used for all statistical analyses.

REFERENCES:

1. Caspersen CJ, Bloemberg BP, Saris WH, Merritt RK, Kromhout D (1991) The prevalence of selected physical activities and their relation with coronary heart disease risk factors in elderly men: the Zutphen Study, 1985. Am J Epidemiol 133: 1078-1092.
2. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR, Jr., et al. (2011) 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc 43: 1575-1581.
3. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol.* 2010;25(9):603-605.
4. Chene G, Thompson SG. Methods for summarizing the risk associations of quantitative variables in epidemiologic studies in a consistent form. *Am J Epidemiol.* 1996;144(6):610-621.
5. Thompson SG, Sharp SJ: Explaining heterogeneity in meta-analysis: a comparison of methods. Stat Med 1999;18:2693-2708

SUPPLEMENTARY DATA

Supplementary Appendix S2. PRISMA 2009 checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
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
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.	9
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.	9
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.	9-10
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	* (S4 Appendix)
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).	9-10
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.	10-11
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	10-11
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.	10

SUPPLEMENTARY DATA

Section/topic	#	Checklist item	Reported on page #
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	10-11
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.	10-11
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).	10-11
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
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.	13, S1 Figure.
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.	13 and S2 Table
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 and Table S2
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.	13-14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	14
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	14
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).	15
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.	15-19
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.	2-3

SUPPLEMENTARY DATA

Supplementary Appendix S3. MOOSE checklist

Criteria		**Brief description of how the criteria were handled in the meta-analysis**
Reporting of background should include		
√	Problem definition	The menopause transition is marked by changes in hormonal patterns, including a marked decline in endogenous estradiol levels, leading to a period of relative androgen excess1. This shift in hormonal balance contributes to an increase in visceral adiposity that is associated with glycemic traits, and therefore may be associated with the risk of type 2 diabetes (T2D). To date, no large studies have examined simultaneously the association of T2D with SHBG, T and E in healthy postmenopausal women.
√	Hypothesis statement	Endogenous sex hormone levels are associated with the risk of T2D.
√	Description of study outcomes	Incidence of T2D
√	Type of exposure or intervention used	Total estradiol (TE), total testosterone (TT) and sex-hormone binding globulin (SHBG) were measured. Free androgen index (FAI) was calculated as ratio of TT to SHBG concentration
√	Type of study designs used	Studies were sought if they (i) were observational cohort, case-cohort studies, or prospective nested case control studies; (ii) had reported on at least one of the sex hormones as exposures: SHBG, TT, BT, TE and bioavailable estradiol (BE); and (iii) had assessed associations with risk of T2D in women (pre and postmenopausal).
√	Study population	Only studies carried out in women.
Reporting of search strategy should include		
√	Qualifications of searchers	The credentials of the investigators are indicated in the authors list.
√	Search strategy, including time period included in the synthesis and keywords	Search strategy and time periods are detailed in page 8 of the manuscript and in S4 Appendix.
√	Databases and registries searched	Embase, Medline, Web-of-Science, PubMed, Cochrane and Google Scholar.
√	Search software used, name and version, including special features	We did not employ a search software. EndNote was used to merge retrieved references and eliminate duplicates.
√	Use of hand searching	We hand-searched bibliographies of retrieved papers and systematic reviews for additional references.
√	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the flow chart. Citations for the included studies are enclosed with the S1 Table and S5 Appendix. The citation list for excluded studies is available upon request.
√	Method of addressing articles published in languages other than English	We placed no restrictions on language; local scientists fluent in the original language of the article were contacted for translation.
√	Method of handling abstracts and unpublished studies	No unpublished studies were identified
√	Description of any contact with authors	We contacted authors of papers if we could not find full texts.
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria were described in the methods section.
√	Rationale for the selection and coding of data	A predesigned data abstraction form was used to extract relevant information. This included questions on study size; study design;

		baseline population; location; age at baseline; duration of follow-up (for cohort studies) and menopausal status.
√	Assessment of confounding	Confounding was not assessed.
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Study quality was assessed based on the nine-star Newcastle–Ottawa Scale(NOS)23 using three pre-defined domains namely: selection of participants (population representativeness), comparability (adjustment for confounders), and ascertainment of outcomes of interest. The NOS assigns a maximum of four points for selection, two points for comparability, and three points for outcome. Nine points on the NOS reflects the highest study quality.
√	Assessment of heterogeneity	Heterogeneity was assessed using the Cochrane χ2 statistic and the I2 statistic.
√	Description of statistical methods in sufficient detail to be replicated	Description of methods of systematic review and assessment of publication bias are detailed in the methods.
√	Provision of appropriate tables and graphics	We included 2 main tables, 3 main Figures, 2 supplementary tables and 2 supplementary Figures.
Reporting of results should include		
√	Graph summarizing individual study estimates and overall estimate	Figure 1-3
√	Table giving descriptive information for each study included	Table 1 and S1-S2 Tables
√	Results of sensitivity testing	NA
√	Indication of statistical uncertainty of findings	NA
Reporting of discussion should include		
√	Quantitative assessment of bias	NA
√	Justification for exclusion	It is specified in the Supplementary S1 Figure.
√	Assessment of quality of included studies	NA
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	
√	Generalization of the conclusions	The generalisability of our findings has been enhanced by the involvement of data from 12 studies.
√	Guidelines for future research	Further studies are needed to establish hormones thresholds at which diabetes risk is increased, because this may aid in identifying high-risk postmenopausal women in the clinical setting. Also, future studies are needed to investigate the effect of medication or lifestyle factors the affect sex hormone levels on glucose metabolism and T2D, which may help in development of novel glucose-lowering therapies and diabetes prevention.
√	Disclosure of funding source	Funding/Support: This study was sponsored and funded by Metagenics Inc. Role of the Funder/Sponsor: Metagenics Inc. had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review or approval of the manuscript. The funder/sponsor did not have the ability to veto publication of study results. Acknowledgements: TM, LJ and OHF work in ErasmusAGE, a center for aging research across the life course funded by Nestlé Nutrition (Nestec Ltd.), Metagenics Inc. and AXA. TM and LJ reported receiving research support from Metagenics.Inc. JN has been financially supported by Erasmus Mundus Western Balkans (ERAWEB), a

		project funded by the European Commission. MK is supported by the AXA Research Fund. OHF reported receiving grants or research support from Metagenics Inc. These funding sources had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review or approval of the manuscript. C. Meun, W.M. Bramer, A. Hofman and J.S.E. Laven have nothing to disclose.

SUPPLEMENTARY DATA

Supplementary Appendix S4 . Search strategy

Embase.com

('sex hormone'/de OR androgen/de OR 'androgen blood level'/de OR 'androgen deficiency'/de OR testosterone/de OR 'testosterone blood level'/de OR 'sex hormone binding globulin'/de OR estradiol/de OR 'estradiol blood level'/de OR hypogonadism/exp OR 'gonad dysfunction'/de OR 'ovary insufficiency'/exp OR 'testis function'/de OR 'hyperandrogenism'/exp OR (((sex OR sexual OR gonad* OR testicular* OR ovar*) NEXT/3 hormone*) OR androgen* OR hyperandrogen* OR hypoandrogen* OR testosterone* OR estradiol* OR oestradiol* OR hypogonad* OR hypergonad* OR ((gonad OR testis OR testes OR testicular OR ovar*) NEAR/3 (dysfunction* OR insufficien* OR failure* OR hypofunct* OR function*))):ab,ti) AND ('non insulin dependent diabetes mellitus'/exp OR (((diabet* OR dm) NEAR/3 ('type 2' OR type2 OR 'type ii' OR 'non insulin' OR noninsulin OR 'adult onset' OR 'slow onset' OR 'maturity onset')) OR T2DM OR dmt2 OR dm2 OR T2-DM OR dm-t2 OR dm-2 OR niddm OR nid-dm):ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim)

Medline ovid

("Gonadal Steroid Hormones"/ OR androgens/ OR testosterone/ OR "Sex Hormone-Binding Globulin"/ OR estradiol/ OR hypogonadism/ OR "hyperandrogenism"/ OR (((sex OR sexual OR gonad* OR testicular* OR ovar*) ADJ3 hormone*) OR androgen* OR hyperandrogen* OR hypoandrogen* OR testosterone* OR estradiol* OR oestradiol* OR hypogonad* OR hypergonad* OR ((gonad OR testis OR testes OR testicular OR ovar*) ADJ3 (dysfunction* OR insufficien* OR failure* OR hypofunct* OR function*))).ab,ti.) AND ("Diabetes Mellitus, Type 2"/ OR (((diabet* OR dm) ADJ3 ("type 2" OR type2 OR "type ii" OR "non insulin" OR noninsulin OR "adult onset" OR "slow onset" OR "maturity onset")) OR T2DM OR dmt2 OR dm2 OR T2-DM OR dm-t2 OR dm-2 OR niddm OR nid-dm).ab,ti.) NOT (exp animals/ NOT humans/) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt.

Cochrane

((((sex OR sexual OR gonad* OR testicular* OR ovar*) NEXT/3 hormone*) OR androgen* OR hyperandrogen* OR hypoandrogen* OR testosterone* OR estradiol* OR oestradiol* OR hypogonad* OR hypergonad* OR ((gonad OR testis OR testes OR testicular OR ovar*) NEAR/3 (dysfunction* OR insufficien* OR failure* OR hypofunct* OR function*))):ab,ti) AND ((((diabet* OR dm) NEAR/3 ('type 2' OR type2 OR 'type ii' OR 'non insulin' OR noninsulin OR 'adult onset' OR 'slow onset' OR 'maturity onset')) OR T2DM OR dmt2 OR dm2 OR T2-DM OR dm-t2 OR dm-2 OR niddm OR nid-dm):ab,ti)

Web-of-science

TS=(((((sex OR sexual OR gonad* OR testicular* OR ovar*) NEAR/2 hormone*) OR androgen* OR hyperandrogen* OR hypoandrogen* OR testosterone* OR estradiol* OR oestradiol* OR hypogonad* OR hypergonad* OR ((gonad OR testis OR testes OR testicular OR ovar*) NEAR/2 (dysfunction* OR insufficien* OR failure* OR hypofunct* OR function*)))) AND ((((diabet* OR dm) NEAR/2 ("type 2" OR type2 OR "type ii" OR "non insulin" OR noninsulin OR "adult onset" OR "slow onset" OR "maturity onset")) OR T2DM OR dmt2 OR dm2 OR T2-DM OR dm-t2 OR dm-2 OR niddm OR nid-dm)) NOT ((animal* OR rat OR rats OR mouse OR mice OR murine OR nonhuman* OR primate*)

SUPPLEMENTARY DATA

NOT (human* OR patient*))) AND DT=(article)

Pubmed publisher

("Gonadal Steroid Hormones"[mh] OR androgens[mh] OR testosterone[mh] OR "Sex Hormone-Binding Globulin"[mh] OR estradiol[mh] OR hypogonadism[mh] OR "hyperandrogenism"[mh] OR (((sex OR sexual OR gonad*[tiab] OR testicular*[tiab] OR ovar*[tiab]) AND hormone*[tiab]) OR androgen*[tiab] OR hyperandrogen*[tiab] OR hypoandrogen*[tiab] OR testosterone*[tiab] OR estradiol*[tiab] OR oestradiol*[tiab] OR hypogonad*[tiab] OR hypergonad*[tiab] OR ((gonad OR testis OR testes OR testicular OR ovar*[tiab]) AND (dysfunction*[tiab] OR insufficien*[tiab] OR failure*[tiab] OR hypofunct*[tiab] OR function*[tiab])))) AND ("Diabetes Mellitus, Type 2"[mh] OR (((diabet*[tiab] OR dm) AND ("type 2" OR type2 OR "type ii" OR "non insulin" OR noninsulin OR "adult onset" OR "slow onset" OR "maturity onset")) OR T2DM OR dmt2 OR dm2 OR T2-DM OR dm-t2 OR dm-2 OR niddm OR nid-dm)) NOT (animals[mh] NOT humans[mh]) NOT (letter[pt] OR news[pt] OR comment[pt] OR editorial[pt] OR congresses[pt] OR abstracts[pt]) AND publisher[sb]

Google scholar

"sex|gonadal|testicular|ovarian hormone|hormones"|androgen|hyperandrogenism|hypoandrogenism|testosterone|estradiol|hypogonadism diabetes "type 2|ii"|"non insulin"|noninsulin|"adult onset"|"slow onset"|"maturity onset"

SUPPLEMENTARY DATA

Supplementary Appendix S5. References of the articles included in the Systematic Review

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