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Systematic Review

Endogenous Sex Hormones (FSH, Oestradiol, Testosterone and SHBG) and Type 2 Diabetes Risk in Postmenopausal Women: A Systematic Review and Meta-Analysis

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Abstract

Background/Objectives: Menopause is accompanied by substantial changes in endogenous sex hormones that influence metabolic regulation. However, the associations of specific hormones with type 2 diabetes (T2D) risk in postmenopausal women remain inconsistent. This study aimed to quantify the relationships between incident T2D and follicle-stimulating hormone (FSH), oestradiol, testosterone, and sex hormone-binding globulin (SHBG), and to examine cross-sectional differences in hormone concentrations between postmenopausal women with and without T2D. Methods: MEDLINE, Embase and Cochrane CENTRAL were searched from database inception to 21 June 2024. Eligible studies included prospective cohort, nested case–control and case–control designs. Associations with incident T2D were pooled using Hartung–Knapp–Sidik–Jonkman random-effects meta-analysis. Both categorical and continuous estimates were extracted, prioritising maximally adjusted models. Risk of bias was assessed using ROBINS-E and the Newcastle–Ottawa Scale. Results: Sixteen studies (18 articles; n = 16,180) were included. Higher SHBG was consistently associated with lower T2D risk in cohort analyses (RR 0.55; 95% CI 0.38–0.72; $I^2 \approx 0\%$). Higher FSH was also associated with lower risk (high vs. low: HR 0.55, 95% CI 0.29–0.81), although continuous estimates showed heterogeneity. Higher oestradiol was associated with increased T2D risk (RR 1.61, 95% CI 1.18–2.03; $I^2 \approx 6\%$), while testosterone was not significantly associated with incident T2D (RR 1.11, 95% CI 0.73–1.50). Cross-sectional analyses indicated lower SHBG and higher testosterone in women with T2D. Conclusions: Endogenous hormone profiles and SHBG concentrations are associated with T2D in postmenopausal women, with the most consistent evidence for an inverse association between SHBG and incident T2D. Because the available evidence is observational and partly heterogeneous, these findings should be interpreted as associations rather than causal or clinically predictive effects. Standardised measurement, repeated pre-diagnostic sampling and external validation are required before these biomarkers can be considered for routine risk stratification.

Keywords: type 2 diabetes; postmenopausal women; endogenous sex hormones; sex hormone-binding globulin (SHBG); follicle-stimulating hormone (FSH); oestradiol; testosterone; systematic review and meta-analysis; insulin resistance

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1. Introduction

The risk of type 2 diabetes (T2D) increases substantially after menopause, alongside major changes in endogenous hormone profiles [1,2]. Postmenopausal women experience reduced ovarian production of oestradiol and progesterone, with compensatory increases in gonadotropins such as follicle-stimulating hormone (FSH) and luteinising hormone (LH) due to loss of ovarian negative feedback [3–5]. These endocrine changes have been linked to adverse shifts in body composition, insulin sensitivity and glucose homeostasis, all of which may contribute to T2D risk [1,3,6–9].

After menopause, oestradiol production shifts from ovarian secretion to peripheral conversion in adipose and other tissues, altering both the source and local biological actions of oestrogen [10,11]. However, epidemiological evidence relating circulating oestradiol to T2D risk in postmenopausal women remains inconsistent, with some studies reporting positive associations [12–14], whereas others reported no clear relationship [15]. Similar inconsistency has been reported for testosterone [12,13,15–17]. These discrepancies may reflect differences in assay methodology [18], study-specific criteria for defining postmenopausal status, adjustment for adiposity and sex hormone-binding globulin (SHBG), and variation in T2D ascertainment across studies.

By contrast, SHBG has more consistently shown an inverse association with T2D risk [19–23]. Higher SHBG concentrations are associated with greater insulin sensitivity and with lower hepatic fat and metabolic syndrome burden [18,22,24,25]. In addition, longitudinal evidence suggests that lower FSH concentrations may be associated with less favourable metabolic status and greater diabetes risk, although the evidence specific to postmenopausal women is more limited than that for SHBG [26–29].

Previous reviews have generally focused on individual hormonal markers [30], particularly FSH and SHBG [24,31], rather than evaluating multiple endogenous sex hormones within a single analytical framework; for example, recent systematic reviews have examined FSH in isolation without integrating broader hormonal profiles [31,32]. This is an important limitation because oestradiol, testosterone, gonadotropins, and SHBG are biologically interrelated, and their associations with T2D may depend on underlying adiposity, hepatic metabolism and population characteristics. Accordingly, we conducted a systematic review and meta-analysis to evaluate the associations of circulating FSH, oestradiol, testosterone, and SHBG with incident T2D risk in postmenopausal women, and to summarise cross-sectional differences in hormone concentrations between women with and without T2D.

2. Materials and Methods

The systematic review and meta-analysis was prospectively registered in PROSPERO (CRD42024540077) [33] and conducted in accordance with PRISMA 2020 (Figure 1) [34].

The research question was structured using the PICO framework: Population (postmenopausal women), Exposure (circulating endogenous sex hormones and SHBG), Comparator (lower hormone levels or non-diabetic controls), and Outcome (incident T2D or differences in hormone concentrations between women with and without T2D).

The overarching aim of this study was to clarify how ESH (endogenous sex hormones) and SHBG relate to T2D in postmenopausal women. The primary objective was to quantify the prospective associations between baseline concentrations of FSH, oestradiol, testosterone, and SHBG and the subsequent risk of incident T2D. A secondary objective was to evaluate cross-sectional differences in hormone levels between women with and without established T2D. To address these aims, we identified eligible longitudinal cohort and nested case–control studies for the primary analyses of incident T2D, extracted maximally adjusted relative risk estimates per prespecified unit or standard-deviation increase (and,

where available, by exposure categories), and synthesised them using random-effects meta-analysis. In secondary, cross-sectional analyses, we pooled mean differences in hormone and SHBG concentrations between women with and without T2D. Between-study heterogeneity and potential effect modification by study design and geographical region for T2D were examined using subgroup analyses.

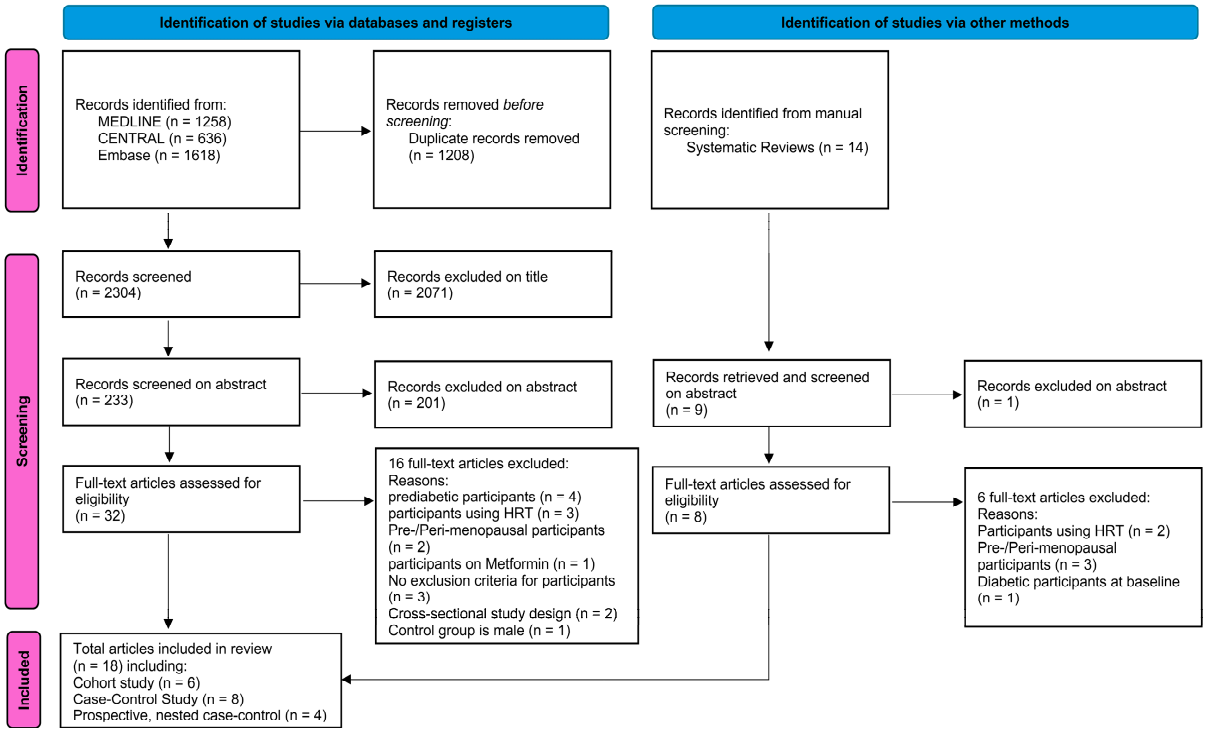

Figure 1. PRISMA diagram.

2.1. Eligibility Criteria

We included observational studies of postmenopausal women that assessed circulating FSH, oestradiol, testosterone, and/or SHBG in relation to T2D. Eligible designs for the primary analysis were prospective cohort studies and nested case–control studies in which participants were free of T2D at baseline and incident T2D was ascertained during follow-up. Eligible designs for secondary cross-sectional analyses were case–control studies comparing postmenopausal women with established T2D with non-diabetic controls. Prospective cohort and nested case–control studies were included in the primary analysis of incident T2D risk, whereas case–control studies were included in secondary analyses comparing hormone concentrations between women with and without existing T2D.

We excluded studies that included or combined pre- or perimenopausal women because the menopausal transition is characterised by large, fluctuating changes in endogenous hormone levels and diabetes risk, rendering these populations not directly comparable to postmenopausal women and unsuitable for adjustment as a simple covariate. We also excluded studies with unstratified hormone therapy use, defined as those that did not report results separately for users and non-users (or by type/regimen of therapy), because exogenous hormones substantially alter circulating endogenous hormone and SHBG concentrations and would therefore confound the associations of interest. Studies were considered to have insufficient outcome data when they did not provide the number of incident T2D cases, person–time at risk, or effect estimates with corresponding measures of variability required to calculate relative risks and 95% CIs. Cross-sectional designs were excluded from the incidence analyses because they do not establish the temporal sequence between hormone measurements and onset of T2D and thus cannot yield valid risk esti-

mates. Ethnically diverse study populations were retained to enhance the generalisability of the findings, and region-based subgroups were prespecified to explore and account for potential geographic and ethnic heterogeneity in the observed associations.

2.2. Data Sources and Search Strategy

We searched MEDLINE, Embase, and Cochrane CENTRAL from database inception to 21 June 2024 using controlled vocabulary and free-text terms related to the postmenopausal state, FSH, oestradiol, testosterone, SHBG, and T2D. The full database-specific search strategies are provided in Supplementary Materials. We also screened the reference lists of included studies and relevant systematic reviews for additional eligible records. Searches were limited to human studies and English-language publications because resources for translation were not available; however, reference lists of relevant reviews and articles were screened to minimise potential language bias.

2.3. Outcomes and Definitions

The primary outcomes were the associations of FSH, oestradiol, testosterone, and SHBG with incident T2D, expressed as relative risks (RRs) with 95% confidence intervals (CIs). Exposures were parameterised as categorical contrasts (e.g., highest vs. lowest quantile, or thresholds such as FSH $\geq$ 50 IU/L) and as continuous effects (per standard-deviation increase). The secondary outcomes were cross-sectional mean differences in these biomarkers between women with and without T2D. Because there were substantial differences between studies in baseline risk, length of follow-up and methods of T2D ascertainment, we did not pool absolute T2D incidence rates across studies and instead focused on synthesising relative measures of association.

2.4. Study Selection and Data Extraction

Two reviewers independently screened titles/abstracts and full texts and independently extracted data using a piloted form. Disagreements were resolved through discussion and, when necessary, consultation with a third reviewer. When multiple publications reported results from the same cohort, the report with the most complete data or longest follow-up was included to avoid double-counting participants. Data were extracted using a prespecified form, including author and year of publication, country/region, study design, sample size, age, ethnicity, diagnostic criteria for T2D and menopause status, adjusted effect estimates with 95% CIs, covariates, timing of sampling relative to T2D onset, and risk-of-bias judgements. For T2D diagnosis, we recorded whether studies used World Health Organisation (WHO), American Diabetes Association (ADA) or other national criteria and noted that diagnostic thresholds changed in 1997 and again in subsequent guideline updates. When multiple estimates were reported, we prioritised the most fully adjusted model that included key metabolic confounders such as age, adiposity measures (e.g., BMI or waist circumference), and lifestyle factors when available. Sensitivity analyses considered alternative estimates (e.g., less adjusted models, different exposure categorisations or subgroups) where available to assess the robustness of the primary findings.

2.5. Handling of Summary Statistics and Units

When studies reported medians and interquartile ranges, means and standard deviations were estimated using established methods for meta-analysis assuming approximate normality (SD $\approx$ IQR/1.35) [35,36]. When only standard errors (SEs) were available, we derived SD as SE $\times \sqrt{n}$; when 95% CIs were reported, we obtained SE as (upper $-$ lower)/3.92, using the relationship that a two-sided 95% CI corresponds to $\pm 1.96 \times$ SE under a normal approximation [35,37]. To facilitate comparison of absolute hormone levels across studies, we converted reported concentrations to common units where feasible (FSH in IU/L,

oestradiol in pmol/L, total testosterone in nmol/L and SHBG in nmol/L). Reported units were converted to common units where possible; where conversion was not feasible, effects were analysed per study-specific standard deviation (SD) to enable comparability.

These transformations were applied only in the cross-sectional analyses of mean differences in hormone and SHBG concentrations between women with and without T2D, because those analyses required absolute levels. For the primary meta-analyses of associations with incident T2D, we used the relative effect estimates reported by each study without transformation to avoid introducing additional approximation error.

2.6. Risk of Bias Assessment

ROBINS-E was used for cohort designs [38] and the Newcastle–Ottawa Scale (NOS) for case–control studies [39]; robvis provided visual summaries [40]. For NOS comparability, age and adiposity (BMI or waist circumference) were considered primary confounders; glycaemic and lifestyle factors were considered additional confounders when available. High-risk studies were retained for sensitivity analyses.

2.7. Statistical Analysis

The included studies addressed two distinct analytical questions: (1) the association between baseline hormone levels and incident T2D, and (2) differences in hormone concentrations between women with and without existing T2D. Accordingly, meta-analyses were conducted separately for these two analytical frameworks. For the analysis of incident T2D, only prospective cohort and nested case–control studies were included, and effect estimates (hazard ratios [HRs], relative risks [RRs], and odds ratios [ORs]) were extracted. Where sufficient studies reported the same effect measure, pooled analyses were conducted separately by measure. When necessary, ORs were interpreted as approximations of relative risk under the assumption of a relatively low incidence of T2D and were not combined with HRs or RRs unless considered methodologically appropriate [41,42]. For cross-sectional comparisons, case–control studies were included, and pooled analyses were conducted using mean differences or standardised mean differences in hormone concentrations between groups.

Meta-analyses were performed using random-effects models based on the Hartung–Knapp–Sidik–Jonkman approach, applied to log-transformed effect estimates and their corresponding standard errors. This approach was chosen because several hormone-specific analyses included a small number of studies and conventional random-effects confidence intervals can be overly narrow when between-study variance is estimated imprecisely. Statistical heterogeneity was assessed using the I^2 statistic and Cochran's Q test.

When pooling across different effect measures was necessary, HRs and ORs were treated as approximations of RRs under the rare outcome assumption, as the cumulative incidence of T2D was low in most included cohort studies (generally <10%) [41–43]. For cross-sectional comparisons of absolute hormone concentrations, values were converted to common units where feasible and pooled as mean differences (MDs) with 95% confidence intervals.

Between-study heterogeneity was assessed using the I^2 statistic, with predefined thresholds used to interpret the magnitude of heterogeneity [44]. Prespecified subgroup analyses, where sufficient studies were available, examined study design, region, and risk of bias. Sensitivity analyses excluded studies at high risk of bias and compared alternative parameterisations of the exposures (per-SD vs. categorical contrasts). Publication bias was not formally assessed because fewer than 10 studies contributed to any individual meta-analysis, which limits statistical power to detect funnel plot asymmetry [45]. All

analyses were performed using Stata version 18. All statistical tests were two-sided, and p values < 0.05 were considered statistically significant.

3. Results

3.1. Characteristics of Included Studies

The study selection process is summarised in the PRISMA flow diagram (Figure 1). The search yielded 3512 records from MEDLINE, Embase and CENTRAL. After removal of duplicates and screening, 18 articles describing 16 unique studies (i.e., 16 non-overlapping study populations) were included (n = 16,180). Where three publications [12,20,22] reported results from the same underlying cohort (e.g., WHI-OS), data were treated as a single study population, and the most comprehensive or relevant dataset was included to avoid duplication.

Study designs comprised six cohort studies (Table 1), eight case–control studies and two prospective nested case–control studies (Table 2). Populations were recruited from Europe, North America and Asia, including predominantly White/European cohorts, multi-ethnic U.S. cohorts, Hispanic/Latina participants, East Asian cohorts and Indian case–control studies. Follow-up among cohort and nested case–control studies ranged from approximately 3 to 10.7 years, while case–control studies varied substantially in sample size, adiposity and glycaemic status. Diagnostic criteria for T2D included ADA and/or WHO definitions based on fasting plasma glucose, HbA1c, oral glucose tolerance test (OGTT), self-report with medication use, prescription records or validated medical records. These differences in population composition, follow-up and case ascertainment were considered when interpreting heterogeneity and when separating prospective from cross-sectional analyses.

Risk of bias was generally low to moderate for cohort studies (Figure 2), while case–control and nested case–control studies were mostly of good or fair quality (Table 3). Most effect estimates came from multivariable models adjusted at least for age and measures of adiposity, with several studies additionally adjusting for SHBG or other hormones.

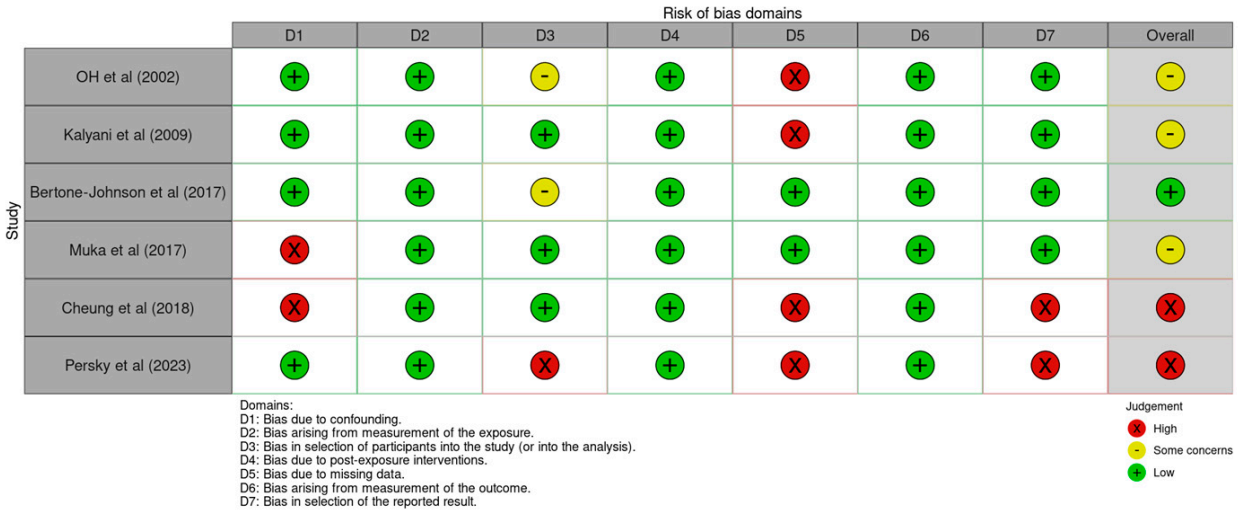

Figure 2. robvis for visualising risk-of-bias assessment of included cohort studies.

Table 1. Baseline characteristics of included cohort studies.

Author, Year	Country	Study/Source of Participants	Design	Year of Baseline Survey	Median Follow-Up (Year)	Population Size	Baseline Mean Age (Year) [1]	Ethnicity	Exclusion Criteria	Menopause Diagnostic Criteria	Diabetes Diagnostic Criteria	Covariates Adjusted
Oh et al. 2002 [14]	USA	Rancho Bernardo Study	Cohort	1984–1987	8	233	72.3 ± 5.4	White	HRT, DM	age > 55	WHO 1999	age, BMI, systolic BP
Kalyani et al. 2009 [13]	USA	MESA	Cohort	2000–2006	4.7	1612	63.11 ± 8.62	White, Black, Hispanic, Chinese	HRT, DM, CVD, missing data	self-reported, bilateral oophorectomy, age > 55	FPG 7.0 mmol/L, prescription records	Adjusted using model 2 criteria, metabolic factors (LDL, HDL, triglycerides, use of lipid-lowering medication, systolic blood pressure, and use of anti-hypertensive medication), behavioural factors (total daily caloric intake, physical activity, and smoking), inflammatory factors (IL-6 and CRP), and reproductive factors (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 or oral contraceptive pill).
Bertone-Johnson et al. 2017 [26]	Finland	KIHD	Cohort	1998–2001	8	514	70.7 ± 6.5	Finnish	HRT, no FSH data	absence of menses for >12 months	self-reported, hospital records; FPG 7.0 mmol/L, 2-h PG 11.1 mmol/L, prescription records	model 1—adjusted for age at baseline (continuous), year of study entry (continuous), oestradiol (continuous), and testosterone (continuous); model 2—adjusted for model 1 covariates plus body mass index at baseline (continuous) and waist-to-hip ratio at baseline (continuous); model 3—adjusted for model 2 covariates plus smoking status at baseline, total pack-years at baseline, age at menopause (continuous), parity (continuous), duration of HT use at baseline, physical activity at baseline (MET, continuous), alcohol use at baseline (g/wk, continuous), systolic and diastolic blood pressure at baseline (continuous), triglycerides, LDL and HDL cholesterol at baseline (ln transformed, all continuous)
Muka et al. 2017 [15]	The Nether-lands	Rotterdam Study	Cohort	1990–1993, 2000–2001, 2006	9.2	3639	66.9 ± 9.6	European	DM, missing data, non-natural menopause	absence of menses for >12 months	WHO 2006, prescription records	adjusted for age, cohort, fasting status, insulin, glucose, and BMI, alcohol intake, smoking status, coronary heart disease, serum total cholesterol, statin use, systolic blood pressure, treatment for hypertension, hormone replacement therapy, age of menopause, CRP, and sex hormones for each other.
Cheung et al. 2018 [27]	HK, China	HKOS	Cohort	1995–2010	10.7	1274	65.90 ± 10.07	Chinese	DM, missing data	-	ICD-9 code 250, prescription records, HbA1c 6.5%, FPG 7.0 mmol/L	Adjusted for age, BMI, smoking status, drinking status, physical activity, history of lipid-lowering and anti-hypertensive medications, history of early menopause, oophorectomy, and hysterectomy, serum oestradiol and calcium, reproductive lifespan, age at menopause, duration of menopause, number of full-term parity, ever use of oral contraceptives, and ever use of hormone replacement therapy.

Table 1. *Cont.*

Author, Year	Country	Study/Source of Participants	Design	Year of Baseline Survey	Median Follow-Up (Year)	Population Size	Baseline Mean Age (Year) [1]	Ethnicity	Exclusion Criteria	Menopause Diagnostic Criteria	Diabetes Diagnostic Criteria	Covariates Adjusted
Persky et al. 2023 [46]	USA	HCHS/SOL	Cohort	2008–2011	6	693	59.32 ± 18.22	Hispanic/ Latino	HRT, pre-/peri-menopausal status	self-reported, FSH & LH measurement	FPG 7.0 mmol/L, 2-h PG 11.1 mmol/L, HbA1c 6.5%, self-reported	Model adjusted for age, BMI, waist to hip ratio, Hispanic background, acculturation score-MESA, recruitment site, education, statin medication use, family history of diabetes, gestational diabetes, cigarette use, alcohol use, physical activity, hypertension, high triglycerides, low HDL, and CRP.

[1] Data are mean ± SD unless otherwise specified.

Table 2. Baseline characteristics of included case–control and prospective, nested case–control studies [1].

Author, Year	Country	Study/Source of Participants	Design	Follow-Up (Year)	Ethnicity	Size (Case vs. Control)	Mean Age (Year)	Exclusion Criteria	Diabetes Diagnostic Criteria	BMI (kg/m^2)	Waist/Hip Ratio	Waist Circum-ference (cm)	FPG (mmol/L)	2 h PG (mmol/L)
Haffner, et al. 1993 [23]	USA	SAHS	Case-control	8	Mexican American, White	19 vs. 42	53.3 ± 1.8 vs. 52.5 ± 1.1	-	WHO 1980	30.1 ± 1.6 vs. 29.2 ± 0	-	-	5.6 ± 0.1 vs. 5.0 ± 0.1	7.9 ± 0.4 vs. 6.1 ± 0.3
Anderson, et al. 1994 [47]	Sweden	Goteborg	Case-control	-	Swedish	39 vs. 17	62 ± 1 vs. 60 ± 1	HRT, PCOS	-	28.3 ± 0.01 vs. 26.8 ± 0.01	0.90 ± 0.01 vs. 0.86 ± 0.02	94.9 ± 1.7 vs. 88.9 ± 3.0	8.6 ± 0.4 vs. 4.4 ± 0.2	-
Phillips, et al. 2000 [48]	USA	NMSS	Case-control	3	Hispanic	20 vs. 29	65.6 ± 0.9 vs. 66.8 ± 0.8	HRT, insulin, lipid-lowering drugs, risk factors for CHD	FPG 7.1 (mmol/L), oral hypogly-caemic agent, history of diabetes	28.9 ± 0.86 vs. 28.9 ± 0.81	0.93 ± 0.02 vs. 0.86 ± 0.02	-	-	-
Ding, et al. 2007 [12] Ding, et al. 2009 [22]	USA	WHI-OS	Prospective, nested case-control	10	White	359 vs. 359	60.3 ± 6.1 vs. 60.3 ± 6.1	HRT, DM, CVD, Cancer	self-reported matched with ADA1997	30.9 ± 6.1 vs. 26.0 ± 4.9	-	-	-	-
Chen, et al. 2012 [20]	USA	WHI-OS	Prospective, nested case-control	5.9	Blacks, Hispanic, Asian/Pacific Islanders	642 vs. 1286	Blacks: 60.9 ± 6.7 vs. 61.0 ± 6.8 Hispanics: 59.9 ± 6.8 vs. 60.1 ± 6.6 Asians: 64.0 ± 7.8 vs. 63.5 ± 7.7	DM, CVD	self-reported, prescription	Blacks: 33.7 ± 7.8 vs. 29.7 ± 6.2 Hispanics: 31.3 ± 6.1 vs. 27.7 ± 5.2 Asians: 26.8 ± 4.2 vs. 23.9 ± 4.5	Blacks: 0.86 ± 0.08 vs. 0.80 ± 0.07 Hispanics: 0.86 ± 0.10 vs. 0.81 ± 0.07 Asians: 0.87 ± 0.07 vs. 0.80 ± 0.06	Blacks: 98.0 ± 15.4 vs. 87.6 ± 13.1 Hispanics: 93.7 ± 15.8 vs. 83.5 ± 11.2 Asians: 84.6 ± 10.1 vs. 75.7 ± 9.7	-	-
Goto, et al. 2012 [21]	Japan	Saku Cohort	Case-control	4	Japanese	85 vs. 85	63.2 ± 7.0 vs. 63.2 ± 7.0	Age <50 or >80, missing data, IGT or IFG	WHO 1999, diagnosed by doctors	24.0 ± 3.7 vs. 21.5 ± 2.6	-	85.6 ± 8.9 vs. 77.8 ± 8.6	6.9 ± 1.8 vs. 5.3 ± 0.4	-
Hu, et al. 2016 [19]	China	EIMDS	Prospective, nested case-control	5	Chinese	87 vs. 87	60.5 ± 11.0 vs. 59.5 ± 11.1	HRT, DM, Cancer, CVD, liver & kidney impairment, acute infection, endocrine system disease, reproductive age	WHO 1999	24.2 ± 3.3 vs. 22.6 ± 2.6	-	80.0 ± 8.8 vs. 75.7 ± 6.8	4.5 ± 0.6 vs. 4.1 ± 0.5	5.6 ± 1.1 vs. 4.6 ± 1.2

Table 2. *Cont.*

Author, Year	Country	Study/Source of Participants	Design	Follow-Up (Year)	Ethnicity	Size (Case vs. Control)	Mean Age (Year)	Exclusion Criteria	Diabetes Diagnostic Criteria	BMI (kg/m^2)	Waist/Hip Ratio	Waist Circumference (cm)	FPG (mmol/L)	2 h PG (mmol/L)
Aljnabi, et al. 2020 [49]	Iraq	Al-Kindi Hospital	Case-control	-	Arabs	45 vs. 47	61.75 ± 5.83 vs. 60.45 ± 6.04	renal disease, cancer, medication affecting oestrogen or metabolism	attending endocrinology and diabetes centre in Al-Kindi Hospital for diagnosis and treatment	27.619 ± 0.394 vs. 29.618 ± 0.566	-	-	-	-
Alva, et al. 2020 [50]	India	K.S.Hegde Charitable Hospital	Case-control	-	Indian	105 vs. 85	59 ± 23.53 vs. 54 ± 14.11	thyroid disorder, liver & renal disease	-	26.32 ± 5.21 vs. 24.1 ± 3.93	-	-	7.9 ± 2.2 vs. 5.5 ± 0.7	-
Saikia, et al. 2021 [17]	India	Gauhati Medical College Hospital	Case-control	-	Indian	100 vs. 86	64.27 ± 5.81 vs. 63.05 ± 5.24	HRT, T1DM, pancreatic diabetes, maturity onset diabetes of young, latent autoimmune disease of adulthood, history of other endocrine diseases such as thyroid illness, hypopituitarism, hepatic disease, renal dysfunction, on drugs that can cause hyperglycemia, lipid-lowering medications, on insulin, smokers, alcoholism, history of oophorectomy, head and neck surgery, or chemo-radiation	ADA 2018	25.98 ± 3.86 vs. 25.36 ± 4.1	0.81 ± 0.04 vs. 0.78 ± 0.08	86 ± 5.2 vs. 82 ± 5.8	7.3 ± 0.8 vs. 4.4 ± 0.5	-
Alva, et al. 2023 [51]	India	K.S.Hegde Charitable Hospital	Case-control	-	Indian	200 vs. 200	57.3 ± 5.75 vs. 55.7 ± 7.9	hysterectomy, HRT	-	28.9 ± 4.5 vs. 24.3 ± 6.7	0.96 ± 0.041 vs. 0.85 ± 0.038	102 ± 13 vs. 78.8 ± 13.5	8.8 ± 3.5 vs. 5.4 ± 0.8	-

[1] Data are mean ± SD unless otherwise specified.

Table 3. NOS for risk-of-bias assessment of included case–control studies.

Author	Year	Selection			Comparability		Exposure			Total Score (Out of 9)
		Adequate Definition of Patient Cases	Representativeness of Patient Cases	Selection of Controls	Definition of Controls	Control for Important or Additional Factors	Ascertainment of Exposure	Same Method of Ascertainment for Participants	Nonresponse Rate	
Haffner et al. [23]	1993	*	*	*	*	*	*	*		7
Andersson et al. [47]	1994	*	*	*		*				4
Phillips et al. [48]	2000	*	*	*		**	*	*	*	8
Ding et al. [12,22]	2007, 2009	*	*	*	*	**	*	*	*	9
Chen et al. [20]	2012	*	*	*	*	**	*	*	*	9
Goto et al. [21]	2012	*	*	*	*	**	*	*	*	9
Hu et al. [19]	2016	*	*	*	*	*	*	*	*	8
Aljnabi et al. [49]	2020	*	*	*	*	**	*	*	*	9
Alva et al. [50]	2020	*				**	*		*	5
Saikia et al. [17]	2021	*	*	*	*	**	*	*	*	9
Alva et al. [51]	2023	*				**	*	*	*	6

NOS, Newcastle-Ottawa scale, * = 1 score; Studies are rated from 0–9, with those studies rating 0–2 (poor quality), 3–5 (fair quality), 6–9 (good/high quality).

Six cohort studies contributed data on incident T2D. Because studies differed substantially in baseline population risk, follow-up duration, and diagnostic criteria, we did not pool absolute incidence rates across studies. Instead, we summarised incidence rates descriptively and focused the meta-analysis on relative measures of association (RR, HR, or OR), which are less sensitive to differences in baseline risk between populations. Where multiple effect measures were reported, analyses were preferentially stratified by study design and effect measure; combined analyses were undertaken only for comparable exposure contrasts and were checked in sensitivity analyses restricted by design or effect measure where feasible.

3.2. FSH and Incident T2D Risk

Two prospective cohort studies examined the association between circulating FSH and incident T2D. Because both studies reported hazard ratios, pooled estimates are presented as HR. Higher FSH concentrations (≥50 IU/L versus lower levels) were associated with lower T2D risk (pooled HR 0.55, 95% CI 0.29–0.81; $I^2 \approx 0\%$) (Figure 3). When FSH was analysed as a continuous exposure, each SD increase in FSH was also associated with lower risk (HR 0.87, 95% CI 0.61–1.13), although heterogeneity between the two studies was high ($I^2 \approx 81\%$) (Figure 4). Given that only two studies contributed to this analysis, the pooled estimate should be interpreted cautiously and regarded as suggestive rather than definitive. The marked heterogeneity in the continuous analysis likely reflects differences in FSH distributions, assay methods and covariate adjustment between the two cohorts (e.g., varying adjustment for adiposity and other metabolic risk factors) [18,26,27,29].

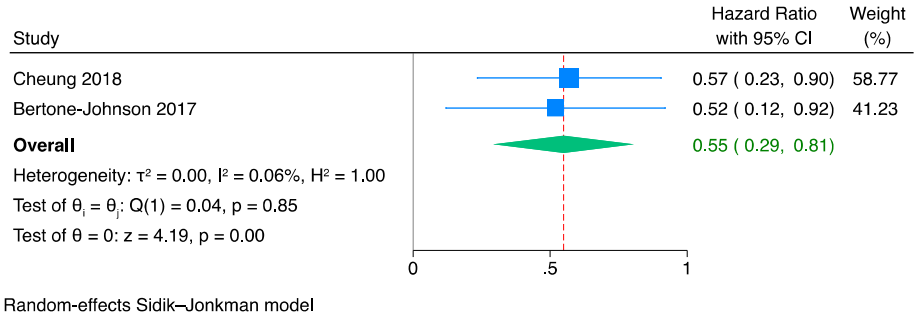

Figure 3. Forest plot of FSH levels (categorical) versus T2D risk [26,27].

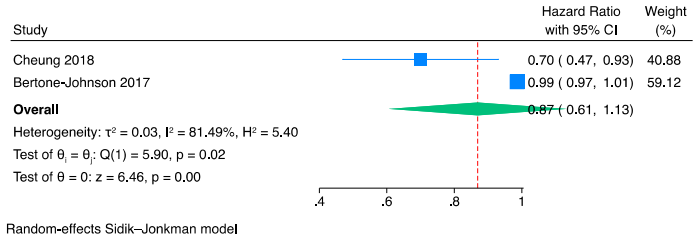

Figure 4. Forest plot of FSH levels (continuous/per SD change) versus T2D risk [26,27].

3.3. Oestradiol and Incident T2D Risk

Five studies assessed the association between serum oestradiol and incident T2D. Per-SD increases in oestradiol (pmol/L) were significantly associated with higher T2D risk (RR 1.61, 95% CI 1.18–2.03), with low between-study heterogeneity ($I^2 \approx 6\%$) (Figure 5). The direction and magnitude of association were consistent across geographical regions and were robust in sensitivity analyses excluding studies at higher risk of bias [12–15,18].

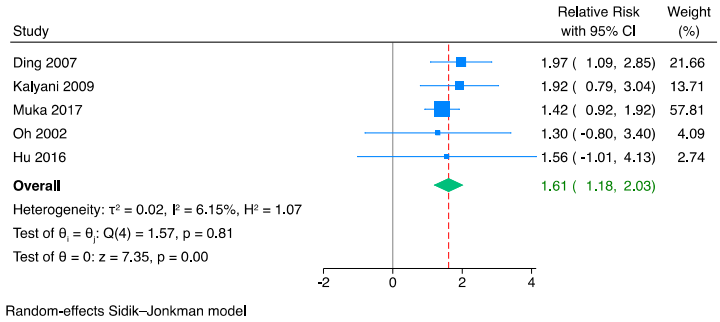

Figure 5. Forest plot of oestradiol levels versus T2D risk [12–15,18].

3.4. Testosterone and Incident T2D Risk

The pooled association between total testosterone (nmol/L, per SD) and incident T2D suggested a modest, statistically non-significant positive relationship (RR 1.11, 95% CI 0.73–1.50; $I^2 \approx 22\%$) (Figure 6). Variation in adjustment strategies—particularly whether models adjusted for SHBG, other sex hormones or markers of adiposity—appeared to contribute to the observed between-study variability [12,14,15,18,21,52].

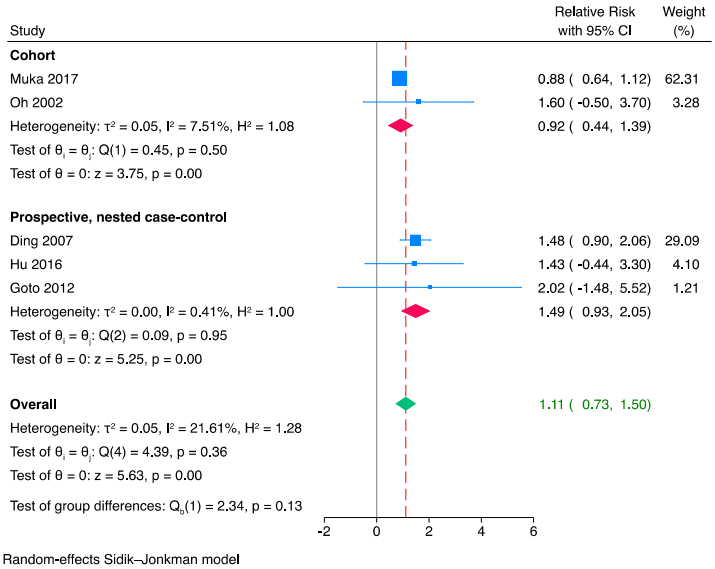

Figure 6. Forest plot of testosterone levels versus T2D risk [12,14,15,18,21,52].

3.5. SHBG and Incident T2D Risk

Six studies reported associations between circulating SHBG (nmol/L) and incident T2D. When all designs were combined, higher SHBG levels were associated with a lower T2D risk (RR 0.24, 95% CI 0.07–0.42) (Figure 7), although heterogeneity was high ($I^2 \approx 88\%$). Subgroup analyses by design showed that in cohort studies alone, each SD increase in SHBG was associated with a 45% RR reduction (RR 0.55, 95% CI 0.38–0.72) with negligible heterogeneity ($I^2 \approx 0\%$), whereas prospective case–control and nested case–control studies showed stronger inverse associations (RR 0.11, 95% CI 0.06–0.15) but with wider variation in sampling and matching strategies. SHBG concentrations varied across studies according to age distribution, statin use and baseline hormone levels, which may partly explain the residual heterogeneity [18,20–22,52].

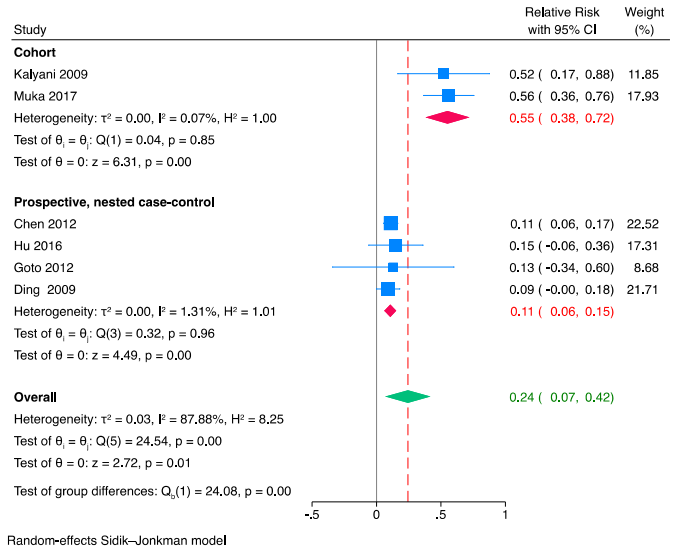

Figure 7. Subgroup analysis: forest plot of SHBG levels versus T2D risk [18,20–22,52].

3.6. Cross-Sectional Differences in Hormone Levels

This section presents results from case–control studies comparing hormone concentrations between postmenopausal women with and without established T2D and should be interpreted separately from prospective risk analyses.

SHBG levels were consistently lower in women with T2D (pooled mean difference −18.43 nmol/L, 95% CI −25.18 to −11.68), with very high heterogeneity ($I^2 \approx 96\%$) (Figure S1 Supplementary Materials). Regional subgroup analyses indicated little or no heterogeneity in East Asian studies, moderate heterogeneity in Indian studies and substantial heterogeneity in U.S. studies, suggesting that population characteristics underlie the variability.

Total testosterone levels were significantly higher in women with T2D than in controls (mean difference + 0.13 nmol/L, 95% CI +0.05 to +0.20; $I^2 \approx 84\%$) (Figure S2 Supplementary Materials). Heterogeneity varied by region, being low in U.S. and Indian cohorts but moderate in East Asian cohorts.

Regarding oestradiol, the pooled mean difference between T2D and non-T2D women was not statistically significant (−23.57 pmol/L, 95% CI −80.94 to +33.81), with extremely high heterogeneity ($I^2 \approx 100\%$) (Figure S3 Supplementary Materials). Excluding one outlying study [49] with markedly divergent oestradiol values attenuated the heterogeneity ($I^2 \approx 80\%$) and shifted the pooled estimate towards a small, non-significant increase in oestradiol among women with T2D (MD + 5.60 pmol/L, 95% CI −2.90 to +14.11) (Figure S4 Supplementary Materials). In these cross-sectional comparisons, reverse causation is

possible: the presence of T2D and its treatments (e.g., insulin, oral hypoglycaemic agents, weight-altering medications) may alter hormone and SHBG levels, making it difficult to infer the direction of causality [21–23,48,51,53]. Accordingly, these cross-sectional pooled mean differences should be interpreted as descriptive summaries of biomarker patterns in established T2D rather than as stable estimates of pre-diagnostic risk. Given the very high between-study heterogeneity and the cross-sectional design, these pooled estimates should be interpreted as exploratory and descriptive rather than as inferential evidence of association. These cross-sectional differences reflect associations with prevalent T2D status and should be interpreted as descriptive phenotypic contrasts rather than evidence of temporal, predictive, or causal relationships.

3.7. Heterogeneity, Subgroup and Sensitivity Analyses

Heterogeneity in hormone-T2D associations varied by analyte and model specification. For oestradiol and cohort-only SHBG analyses, heterogeneity was low ($I^2 \approx 6\%$) and negligible (≈0%), indicating broadly consistent associations across studies. In contrast, heterogeneity was high for per-SD FSH models and for SHBG when all designs were pooled. For FSH, differences in exposure parameterisation (categorical thresholds vs. continuous SDs) appeared to contribute to the variability between studies. For SHBG, combining cohort and case–control designs introduced substantial heterogeneity, which was greatly reduced when analyses were restricted to cohort studies.

Subgroup analyses by region and study design also influenced heterogeneity. For example, studies carried out in the USA tended to show more variable SHBG and testosterone differences than European and East Asian cohorts. Across hormones, the main contributors to heterogeneity appeared to be study design (cohort vs. case–control) and geographical region (Europe, North America, East Asia and India).

Sensitivity analyses excluding higher-risk studies did not materially change the direction of associations across hormones. Alternative exposure parameterisations (per-SD vs. categorical contrasts), examined primarily for FSH, yielded consistent findings. However, for analytes with few studies or substantial heterogeneity, these results should be interpreted as supportive rather than definitive. Sensitivity and subgroup analyses presented in the Supplementary Materials generally supported the direction of the main pooled estimates, although precision was limited for hormones with few contributing studies.

4. Discussion

4.1. Summary of Aims and Main Findings

In this systematic review and meta-analysis, higher SHBG concentrations were consistently associated with lower risk of incident T2D, whereas evidence for oestradiol and testosterone was heterogeneous and less conclusive. Associations for FSH were suggestive but less consistently reported across studies.

Across prospective studies, higher FSH and higher SHBG were generally associated with lower risk of incident T2D, whereas higher oestradiol and higher total testosterone tended to be associated with higher risk. In cross-sectional analyses, women with T2D had markedly lower SHBG and modestly higher testosterone than non-diabetic controls, while differences in oestradiol were small and inconsistent. Importantly, these cross-sectional findings do not establish temporality and may reflect reverse causation, whereby diabetes-related metabolic changes influence circulating hormone levels.

Overall, SHBG showed the most consistent inverse association with incident T2D, FSH showed a more tentative inverse association based on limited data, oestradiol showed a positive association in prospective analyses, and testosterone showed a weaker and less consistent positive association. This pattern is compatible with SHBG acting as a

regulator of sex steroid bioavailability [54,55] and as an integrative marker of metabolic status [25]. In addition, genetic studies have reported that variants influencing circulating SHBG concentrations are also associated with T2D risk, further supporting the relevance of SHBG to broader metabolic pathways involved in glucose regulation [22]. Therefore, associations for testosterone and oestradiol should be interpreted in the context of SHBG, adiposity and hepatic insulin resistance, all of which influence the free or bioavailable fractions of sex steroids.

4.2. Interpretation of Study Design Differences

The findings from prospective and cross-sectional studies should be interpreted differently. Prospective studies assess whether baseline hormone levels are associated with future diabetes risk and therefore provide stronger evidence of temporal relationships. In contrast, case–control studies describe hormone differences in women with established diabetes and may reflect consequences of the disease, obesity, or treatment effects. Accordingly, prospective findings were considered primary, and cross-sectional findings were interpreted as supportive but non-causal.

4.3. FSH and Incident T2D Risk

Limited prospective evidence suggests that higher FSH concentrations in postmenopausal women may be associated with lower cardiometabolic and T2D risk [26,27,29]. Because only two prospective cohort studies contributed to the principal FSH analyses, these findings should be regarded as preliminary and hypothesis-generating rather than definitive. Mechanistically, FSH has been linked to metabolic regulation, including potential effects on pancreatic islet function and broader endocrine–metabolic signalling pathways [56–59], although evidence remains limited and primarily observational. At the same time, FSH trajectories across the menopausal transition are highly variable [60], and our per-SD analyses showed more heterogeneity than threshold-based contrasts. This suggests that broad FSH categories may be more stable for descriptive epidemiology than small within-range changes, but replication is required before clinical interpretation.

Cross-sectionally, women with T2D tended to have slightly lower FSH than controls, but CIs were wide and between-study variation was considerable. Because most cross-sectional samples were obtained after diabetes diagnosis, these differences are difficult to interpret causally. Obesity is associated with lower FSH concentrations in postmenopausal women [60], and experimental metabolic studies suggest that hyperinsulinaemia may suppress gonadotropin secretion [61]; therefore, lower FSH levels in established T2D may reflect downstream metabolic effects rather than causal pathways.

4.4. Oestradiol and Incident T2D Risk

Higher circulating oestradiol was consistently associated with increased incident T2D risk, with little heterogeneity between cohorts. This is notable because oestradiol is generally considered metabolically protective in premenopausal women [11], with established effects on insulin sensitivity and energy balance, yet in late postmenopause, relatively higher oestradiol may reflect greater adipose mass, increased aromatisation, or altered hepatic clearance. Experimental and clinical data support complex, tissue-specific effects of oestradiol on insulin sensitivity, adiposity and hepatic glucose production, which may differ before and after menopause [10,11,54,57,58]. This apparent contrast with findings from exogenous hormone therapy trials [62] may reflect differences between endogenous postmenopausal oestradiol concentrations, which often correlate with adiposity and metabolic dysfunction, and pharmacological oestrogen exposure.

By contrast, cross-sectional differences in oestradiol between women with and without T2D were small and directionally inconsistent and were highly heterogeneous until an

outlying study was excluded. Several factors likely contribute: (i) very low absolute oestradiol concentrations after menopause, where immunoassays have limited sensitivity at low postmenopausal oestradiol concentrations compared with liquid chromatography–tandem mass spectrometry (LC–MS/MS) methods [18,63,64]; (ii) variability in timing of sampling relative to diagnosis and treatment; and (iii) confounding by adiposity and liver fat. More accurate measurement (preferably mass spectrometry) and repeated pre-diagnostic sampling would be needed to disentangle whether higher oestradiol is causally related to T2D or is mainly a correlate of adiposity. Because SHBG strongly influences the free fraction of circulating oestradiol, observed associations between total oestradiol concentrations and T2D risk may partly reflect broader metabolic changes affecting SHBG production, adiposity and hepatic insulin resistance.

4.5. Testosterone and Incident T2D Risk

In prospective analyses, higher total testosterone was associated with a modest but statistically non-significant increase in T2D risk, with low-to-moderate heterogeneity [12,13,15,18]. Several cohorts have reported stronger positive associations that attenuate after adjustment for SHBG or indices of adiposity [12,13,18], suggesting that part of the apparent risk signal from testosterone may actually be mediated or confounded by low SHBG and central adiposity. Our cross-sectional synthesis found higher testosterone levels in women with T2D compared with controls [17,21,23,48,51,53], again with some heterogeneity by region.

These findings are consistent with the broader evidence in women, in whom hyperandrogenaemia, including in conditions such as polycystic ovary syndrome, is associated with insulin resistance and adverse glycaemic risk [3,30,65]. In contrast, lower testosterone concentrations in men are more consistently associated with insulin resistance and T2D risk, suggesting possible sex-specific endocrine–metabolic relationships [66].

4.6. SHBG, Free Hormone Levels and Insulin Resistance

SHBG emerged as the most consistent marker in our review. Higher SHBG was associated with lower incident T2D risk, particularly in cohort studies with careful confounder adjustment, and SHBG levels were substantially lower in women with T2D than in controls. SHBG functions not only as a transport protein but also as a regulator of sex steroid bioavailability, thereby influencing the fraction of biologically active hormone in circulation [24,67,68]. Variation in SHBG concentrations is therefore a key determinant of free androgen and oestrogen exposure in target tissues [24,67,68]. Genetic evidence also supports a link between SHBG biology and T2D: variants associated with higher circulating SHBG have been linked to lower T2D risk, although such evidence should be interpreted alongside observational and metabolic data rather than as proof of a direct clinical intervention target [22,69].

Beyond its effect on free hormones, SHBG is closely linked to insulin resistance and hepatic metabolism [24,67]. Hepatic SHBG production is suppressed in insulin-resistant states, and low SHBG levels track with hepatic steatosis, visceral adiposity and worsening glycaemia [25,67]. Existing mechanistic and prospective evidence suggests that improving insulin sensitivity or reducing liver fat may increase SHBG, while low SHBG is associated with subsequent diabetes independently of body mass index and traditional risk factors [22,24,25]. Our findings are compatible with an association between lower SHBG, hepatic insulin resistance and altered sex steroid bioavailability, although the observational evidence cannot establish causality or directionality.

Although SHBG showed the most consistent association with incident T2D, the observational evidence does not allow distinction between SHBG as a causal factor, a mediator,

or a marker of underlying metabolic processes [22]. Given its strong dependence on hepatic function and insulin resistance, SHBG may partly reflect underlying metabolic status rather than act as an independent causal determinant of T2D risk [25].

4.7. T2D Diagnosis and Implications for Interpretation

The included studies used a mixture of diagnostic criteria for T2D, including fasting plasma glucose, OGTT, HbA1c and validated medical records. Since around 2010, HbA1c has been widely adopted as a diagnostic test because it is convenient and reflects average glycaemia over several months [69,70]. However, HbA1c may miss early T2D [71], is influenced by factors such as red cell turnover, iron status and ethnicity [72,73], and may lag behind changes in insulin resistance. Indices such as HOMA-IR may therefore be more sensitive to early insulin resistance, including in individuals with normal HbA1c [74–76]. In our review, reliance on clinical diagnoses and HbA1c-based definitions may have preferentially identified more advanced or established T2D, which could partly explain why cross-sectional hormone differences appeared more marked than some prospective associations.

4.8. Integrating Longitudinal and Cross-Sectional Findings

Our longitudinal and cross-sectional results are broadly coherent when interpreted together, but they should be interpreted as associations rather than a causal sequence. In the prospective studies, baseline profiles characterised by lower SHBG and FSH and higher oestradiol and testosterone were associated with subsequent incident T2D. Cross-sectionally, established T2D was characterised by lower SHBG and higher testosterone, with less consistent differences in FSH and oestradiol. This pattern is compatible with a model in which hepatic insulin resistance, visceral adiposity and altered sex hormone bioavailability are closely interrelated; however, the direction and mediation of these relationships cannot be determined from the available observational data alone. Reverse causation also remains plausible, because once T2D develops, hyperinsulinaemia, adiposity change and related metabolic disturbances may further modify SHBG and sex hormone levels [25,77,78]. The cross-sectional findings should not be interpreted as evidence of causal or predictive associations, as they are subject to reverse causation and substantial heterogeneity.

4.9. Clinical Implications

The present findings do not support the routine clinical use of endogenous sex hormones or SHBG for T2D screening or risk prediction in postmenopausal women [15,22,71]. However, the consistent inverse association observed for SHBG across prospective studies suggests that SHBG may reflect broader metabolic and hepatic processes relevant to T2D pathophysiology [20–22,67,68]. Interpretation of hormone concentrations should consider adiposity, insulin resistance, liver function and assay variability, all of which influence circulating hormone and SHBG levels [18,20–22,59,64]. At present, substantial heterogeneity in study design, assay methodology and confounder adjustment limits translation into clinical practice. Future prospective studies using standardised hormone assays, repeated pre-diagnostic sampling and SHBG-adjusted modelling are required before these biomarkers can be evaluated for potential incremental value beyond established T2D risk factors.

4.10. Strengths and Limitations

This study addressed a focused clinical question, separated prospective incident T2D analyses from cross-sectional comparisons, and used design-aware synthesis approaches appropriate for heterogeneous observational studies. Reporting followed PRISMA 2020, risk of bias was assessed using ROBINS-E and the Newcastle–Ottawa Scale, and subgroup analyses by study design and region helped clarify sources of heterogeneity. Inclusion of both categorical contrasts and per-SD effects improved comparability across studies,

although per-SD harmonisation reduces direct clinical interpretability because one standard deviation may represent different absolute hormone differences across cohorts and assay platforms.

The main limitations are the observational nature of the evidence, the small number of studies for some hormones, and substantial heterogeneity in several pooled estimates. Residual heterogeneity persisted in mixed-design pools, particularly for SHBG, and was also substantial in cross-sectional analyses of SHBG, testosterone and oestradiol. Coherence improved when analyses were restricted to cohort studies, underscoring the influence of sampling frames, confounding control, assay variation and case ascertainment [18,20–22]. Measurement variability across assays and laboratories limits translation of absolute thresholds into clinical practice; relatively few studies used mass spectrometry for sex steroids, and inter-assay differences likely affected absolute hormone comparisons [18,59,64]. Consequently, some between-study heterogeneity in pooled estimates may reflect analytical measurement variability rather than true biological differences between populations. Most studies reported total rather than free or bioavailable hormone concentrations, so we could not assess whether free testosterone or oestradiol shows different or stronger associations with T2D risk.

Not all studies adjusted for key confounders such as adiposity, hepatic function, insulin resistance or SHBG, which could inflate positive associations for testosterone or attenuate inverse associations for SHBG [18,20–22,67,68,76,79]. For cross-sectional comparisons, post-diagnostic sampling raises the possibility of reverse causation and treatment effects [21–23,48,51,53]. These cross-sectional estimates should therefore be interpreted as exploratory and descriptive rather than as stable quantitative summaries of causal or pre-diagnostic effects. Funnel plots were not formally interpreted because fewer than ten studies contributed to each analysis, limiting statistical power to detect asymmetry [45,80]. Selective reporting of exposure parameterisations also cannot be excluded.

5. Conclusions

In postmenopausal women, higher SHBG was the most consistently observed hormonal correlate of lower incident T2D risk, while higher FSH showed a more tentative inverse association based on limited data. Higher oestradiol showed a relatively consistent positive association with incident T2D across prospective studies, whereas testosterone associations were weaker, less consistent and more sensitive to differences in confounder adjustment. Cross-sectional evidence showed lower SHBG and higher testosterone among women with established T2D, but these findings are susceptible to reverse causation and treatment-related changes.

These findings should be interpreted as observational associations rather than causal evidence or validated clinical prediction tools. Current evidence does not justify using endogenous sex hormones or SHBG for routine T2D screening, surveillance or treatment selection in postmenopausal women. Future studies should prioritise repeated pre-diagnostic hormone measurements, standardised assays, direct measurement of free or bioavailable hormone indices, SHBG-adjusted modelling of sex steroids, consistent adjustment for adiposity and hepatic insulin resistance, and external validation of whether these biomarkers add incremental value beyond established T2D risk models.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/endocrines7020026/s1, Figure S1: Subgroup analysis—forest plot of SHBG level between T2D and non-T2D women; Figure S2: Subgroup analysis—forest plot of testosterone level between T2D and non-T2D women; Figure S3: Forest plot of oestradiol level between T2D and non-T2D women; Figure S4: Sensitivity analysis—forest plot of oestradiol level between T2D and non-T2D women; Search strategies.

Author Contributions: Conceptualisation, C.S.K. and S.R.; methodology, C.C.-Y.L.; literature search, C.C.-Y.L.; study screening and eligibility assessment, C.C.-Y.L., C.S.K. and S.R.; data extraction and curation, C.C.-Y.L., C.S.K. and S.R.; formal analysis, C.C.-Y.L.; writing—original draft preparation, C.C.-Y.L.; writing—review and editing, C.S.K. and S.R.; supervision, C.S.K. and S.R. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ADA	American Diabetes Association
BMI	Body Mass Index
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence Interval
ESH	Endogenous Sex Hormones
FSH	Follicle-Stimulating Hormone
HbA1c	Glycated Haemoglobin
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
HR	Hazard Ratio
I^2	I-squared Statistic
IU/L	International Units Per Litre
LC-MS/MS	Liquid Chromatography–Tandem Mass Spectrometry
MD	Mean Difference
NOS	Newcastle–Ottawa Scale
OGTT	Oral Glucose Tolerance Test
OR	Odds Ratio
PICO	Population, Intervention/Exposure, Comparator, Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
ROBINS-E	Risk Of Bias In Non-randomised Studies of Exposures
RR	Relative Risk
SD	Standard Deviation
SE	Standard Error
SHBG	Sex Hormone-binding Globulin
T2D	Type 2 Diabetes

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