Appendix 1 search strategies

A. Cochrane Library

#1 MeSH descriptor: [Dementia] explode all trees

#2 MeSH descriptor: [Alzheimer Disease] explode all trees

#3 MeSH descriptor: [Cognition Disorders] explode all trees

#4 (dementia or alzheimer):ti,ab,kw (Word variations have been searched)

#5 ((cognitive or cognition) near/1 (decline or defect or deficit or degeneration or deterioration or disorder or dysfunction or fail or function or impairment)):ti,ab,kw (Word variations have been searched)

#6 #1 or #2 or #3 or #4 or #5

#7 MeSH descriptor: [Testosterone] explode all trees

#8 (testosterone or "8 isotestosterone" or adrotest or Andriol or "andro 100" or androderm or androfort or androgel or androlin or andronaq or andropatch or androsorb or androstenolone or "Androtardyl 250" or androtest or androtop or andrusol or aquaviron or Axiron or beta testosterone or "bio t gel" or col 1621 or col1621 or Delatestryl or "depot hormon m" or Fortesa or fortigel or "geno cristaux" or histerone or homosteron or hydroxyandrostenone or Intrinsa or libigel or livensa or mertestate or natesto or Nebido or neotestis or "nsc 9700" or nsc9700 or opterone or "oreton f" or orquisteron or "Pantestone 40" or "percutacrine androgenique" or "percutacrine androgine" or primotest or "Restandol Testocaps" or sterotate or Striant or sustanon or sustenon or synandrol or teslen or testamone or testandrone or testaqua or testerone or testim or Testim or "testo enant" or testoderm or testogel or "testoject

50" or testolin or testoluton or testopel or testosterone or testro or testrone or testryl or Tostran or tostrelle or tostrex or Virormone or virosterone or vogelxo):ti,ab,kw (Word variations have been searched)

#9 MeSH descriptor: [Hypogonadism] explode all trees

#10 hypogonadism:ti,ab,kw (Word variations have been searched)

#11 #7 or #8 or #9 or #10

#12 #6 and #11 in Trials

B. EMBASE

Search Strategy:

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1 exp dementia/

2 exp Alzheimer disease/

3 exp cognitive defect/

4 (dementia* or alzheimer*).tw,kw.

5 (cognit* adj2 (decline* or defect* or deficit* or degenerat* or deteriorat* or disorder* or dysfunction* or fail* or function* or impair*)).tw,kw.

6 or/1-5

7 exp testosterone/

8 (testosterone or "8 isotestosterone" or 8-isotestosterone or adrotest or Andriol or "andro 100" or androderm or androfort or androgel or androlin or andronaq or andropatch or androsorb or androstenolone or "Androtardyl 250" or androtest or

androtop or andrusol or aquaviron or Axiron or beta testosterone or "bio t gel" or col 1621 or col1621 or Delatestryl or "depot hormon-m" or Fortesa or fortigel or "geno cristaux" or histerone or homosteron or hydroxyandrostenone or Intrinsa or libigel or livensa or mertestate or natesto or Nebido or neotestis or "nsc 9700" or nsc9700 or opterone or "oreton f" or orquisteron or "Pantestone 40" or "percutacrine androgenique" or "percutacrine androgine" or primotest* or "Restandol Testocaps" or sterotate or Striant or sustanon or sustenon or synandrol or teslen or testamone or testandrone or testaqua or testerone or testim or Testim or "testo enant" or testoderm or testogel or "testoject 50" or testolin or testoluton or testopel or testosterone? or testro or testrone or testryl or Tostran or tostrelle or tostrex or Virormone or virosterone or vogelxo).mp.

9 exp hypogonadism/

10 hypogonadism.tw,kw.

11 or/7-10

12 6 and 11

13 Clinical study/

14 Case control study/

15 Longitudinal study/

16 Prospective study/

17 Randomized controlled trials/

18 16 not 17

19 Cohort analysis/

20 (Cohort adj (study or studies)).mp.

21 (case control* adj (study or studies)).mp.

22 (follow up adj (study or studies)).tw.

23 (observational adj (study or studies)).mp.

24 or/13-15,18-23

25 12 and 24

C. PubMed

#17 Search (#13 AND #16)

#16 Search (#14 or #15)

#15 Search ("clinical study"[Text Word] OR "clinical studies"[Text Word] OR "case control"[Text Word] OR "case controls"[Text Word] OR longitudinal[Text Word] OR prospective[Text Word] OR "cohort study"[Text Word] OR "cohort studies"[Text Word] OR "cohort analysis"[Text Word] OR "cohort analyses"[Text Word] OR followup[Text Word] OR "follow up"[Text Word] OR "follow-up"[Text Word] OR observational[Text Word])

#14 Search ("Case-Control Studies"[Mesh] OR "Cohort Studies"[Mesh] OR "Clinical Study" [Publication Type] OR "Longitudinal Studies"[Mesh] OR "Prospective Studies"[Mesh] OR "Follow-Up Studies"[Mesh])

#13 Search (#7 AND #12)

#12 Search (#8 or #9 or #10 or #11)

#11 Search hypogonadism[Text Word]

#10 Search Hypogonadism[MeSH Terms]

#9 Search (testosterone[Text Word] OR "8 isotestosterone"[Text Word] OR adrotest[Text Word] OR Andriol[Text Word] OR "andro 100"[Text Word] OR androderm[Text Word] OR androfort[Text Word] OR androgel[Text Word] OR androlin[Text Word] OR andronaq[Text Word] OR andropatch[Text Word] OR androsorb[Text Word] OR androstenolone[Text Word] OR "Androtardyl 250"[Text Word] OR androtest[Text Word] OR androtop[Text Word] OR andrusol[Text Word] OR aquaviron[Text Word] OR Axiron[Text Word] OR beta testosterone[Text Word] OR "bio t gel"[Text Word] OR col 1621[Text Word] OR col1621[Text Word] OR Delatestryl[Text Word] OR "depot hormon m"[Text Word] OR Fortesa[Text Word] OR fortigel[Text Word] OR "geno cristaux"[Text Word] OR histerone[Text Word] OR homosteron[Text Word] OR hydroxyandrostenone[Text Word] OR Intrinsa[Text Word] OR libigel[Text Word] OR livensa[Text Word] OR mertestate[Text Word] OR natesto[Text Word] OR Nebido[Text Word] OR neotestis[Text Word] OR "nsc 9700"[Text Word] OR nsc9700[Text Word] OR opterone[Text Word] OR "oreton f"[Text Word] OR orquisteron[Text Word] OR "Pantestone 40"[Text Word] OR "percutacrine androgenique"[Text Word] OR "percutacrine androgine"[Text Word] OR primotest[Text Word] OR "Restandol Testocaps"[Text Word] OR sterotate[Text Word] OR Striant[Text Word] OR sustanon[Text Word] OR sustenon[Text Word] OR synandrol[Text Word] OR teslen[Text Word] OR testamone[Text Word] OR testandrone[Text Word] OR testaqua[Text Word] OR testerone[Text Word] OR testim[Text Word] OR Testim[Text Word] OR "testo enant"[Text Word] OR

testoderm[Text Word] OR testogel[Text Word] OR "testoject 50"[Text Word] OR testolin[Text Word] OR testoluton[Text Word] OR testopel[Text Word] OR testosterone[Text Word] OR testro[Text Word] OR testrone[Text Word] OR testryl[Text Word] OR Tostran[Text Word] OR tostrelle[Text Word] OR tostrex[Text Word] OR Virormone[Text Word] OR virosterone[Text Word] OR vogelxo[Text Word])

#8 Search Testosterone[MeSH Terms]

#7 Search (#1 or #2 or #3 or #4 or #5 or #6)

#6 Search ("Cognition decline"[Text Word] OR "Cognition defect"[Text Word] OR "Cognition deficit"[Text Word] OR "Cognition deficiency"[Text Word] OR "Cognition degeneration"[Text Word] OR "Cognition deterioration"[Text Word] OR "Cognition disorder"[Text Word] OR "Cognition disorders"[Text Word] OR "Cognition dysfunction"[Text Word] OR "Cognition failure"[Text Word] OR "Cognition impairment"[Text Word])

#5 Search ("Cognitive decline"[Text Word] OR "cognitive defect"[Text Word] OR "cognitive deficit"[Text Word] OR "cognitive deficiency"[Text Word] OR "cognitive degeneration"[Text Word] OR "cognitive deterioration"[Text Word] OR "cognitive disorder"[Text Word] OR "cognitive disorders"[Text Word] OR "cognitive dysfunction"[Text Word] OR "cognitive failure"[Text Word] OR "cognitive impairment"[Text Word])

#4 Search (Dementia*[Text Word] OR Alzheimer*[Text Word])

#3 Search Cognition Disorders[MeSH Terms]

#2 Search Alzheimer Disease[MeSH Terms]

#1 Search Dementia[MeSH Terms]

Appendix2 Summary results from studies cannot be quantitively summarized

Study ID	Key findings
Burkhardt 2006[28]	This study identified a significant interaction between calculated free testosterone (FT) and APOE 4 on general cognition (P= 0.01) and executive functioning, working memory, and attention (P <0.01). The study also found a higher testosterone levels were not associated with better cognitive function in men at increased risk for Alzheimer's disease.
Carr 2018[18]	This study assessed measures of plasma testosterone levels as a biomarker of AD in male participants. Baseline testosterone levels were significantly different between clinical diagnosis groups cognitively normal controls, MCI, or AD], with the lowest testosterone levels in men with AD. Lower baseline testosterone levels were associated with higher baseline clinical severity. Change in testosterone levels between baseline and 1-year follow-up varied by diagnosis; MCI had the greatest decreases in testosterone levels between baseline and 1-year follow-up. Despite differences by clinical

	diagnosis, there was no association between plasma testosterone and CSF biomarkers of AD pathology.
Cherrier 2005[21]	Peak serum total T levels were raised from baseline an average of 295% in the active treatment group. Improvements in spatial memory ($p<0.05$) and constructional abilities ($p<0.05$) and verbal memory were evident in the T group. No changes were noted for selective and divided attention or language. Prostate specific antigen did not significantly change during this brief treatment.
Cunningham 2014[29]	In a low OS environment, testosterone was positively associated with the level of the antioxidant, GST, while no deleterious effects on cognitive function were noted. In contrast, under conditions of high OS (homocysteine levels >12 μM), testosterone and LH were associated with cognitive impairment, but only among Caucasians. The ethnic difference was attributed to significantly higher GST levels among Mexican-Americans.
Fonda 2005[41]	Older age was associated with lower cognitive functioning. In unadjusted models, logged free and total testosterone, DHEA, and DHEAS related to higher functioning in at least one cognitive domain; logged FSH, SHBG, and LH related to lower functioning in at least one cognitive domain; and logged E1, CRT, and PRL were not significant. In adjusted models, logged hormones did not relate to cognitive function except for logged E1 and CRT, which had negative effects.

	Logged hormones did not mediate the age–cognition relationship.
Hogervorst 2004[35]	This study measured gonadotropins (follicle stimulating hormone, FSH, and luteinizing hormone, LH), sex hormone binding globulin (SHBG, which determines the amount of free testosterone) and total -T) using enzyme immunoassays. AD cases had significantly higher LH and FSH and lower free testosterone levels. LH, FSH and SHBG all increased with age, while free testosterone decreased. Low free testosterone was an independent predictor for AD. Its variance was overall explained by high SHBG, low TT, high LH, an older age and low body mass index (BMI). In controls, low thyroid stimulating hormone levels were also associated with low free testosterone. Elderly AD cases had raised levels of gonadotropins. This response may be an attempt to normalize low free testosterone levels. In non-demented participants, subclinical hyperthyroid disease (a risk factor for AD) which can result in higher SHBG levels, was associated with low free testosterone. Lowering SHBG and/or screening for subclinical thyroid disease may prevent cognitive decline and/or wasting in men at risk for AD.
Lee 2010[42]	Total testosterone and free testosterone were associated with higher FC z-scores, LH and FSH with lower FC z-scores in age-adjusted linear regressions. After adjusting for health, lifestyle and center, a modest association was only observed between DHEAS and a lower FC

	z-score (bZK0.011, PZ0.02), although this was driven by subjects with DHEAS levels O10 mmol/l. Locally weighted plots revealed no threshold effects between hormones and FC. There was no association between CAG repeat length and FC z-score after adjustment for age and centre (bZK0.007, PZ0.06), nor any interaction effect between CAG repeat length and hormones.
Lessov 2005[43]	There were no significant associations between sex hormone or SHBG concentrations and performance on a series of cognitive tasks measuring global and executive function, visual and verbal learning and memory. Higher midlife T concentrations were associated with larger hemispheric, frontal, and parietal regional brain volumes and with smaller left occipital brain volume. Higher estradiol and estrone concentrations were also associated with smaller right (estradiol) and both right and left (estrone) occipital volumes, but with no other brain regions. Owing to the multiple comparisons conducted, some significant associations may have occurred by chance.
Muller 2005[44]	Curvilinear associations were observed between T and memory performance and processing capacity/speed, suggesting optimal sex hormone levels. No association between E2 and cognitive functioning was found. After the population was subdivided into four age decades, a linear association of T with cognitive functioning in the oldest age category remained. No association was found in the other age decades.

	Lower bioavailable T levels were associated with lower scores on processing capacity/speed and executive function; (95% CI) values were 0.36 (0.07 to 0.66) and 0.17 (0.01 to 0.35). Similar results were observed for total T.
Pennanen 2004[45]	This study showed AD patients had higher levels of serum total (P=0.02) and free testosterone (P<0.001), and higher free androgen index (FAI) (P=0.02) compared to cognitively normal controls. No differences were found for the SHBG levels. These data provide no support for hypotheses of (disproportionally) decreased levels of serum testosterone in AD. These data also show that all cognitively normal controls had an FAI below the normal range.
Takayanagi 2015[46]	Higher levels of serum sex hormone binding globulin (SHBG) were associated with lower delayed verbal memory scores [standardized coefficients (beta) = −0.19, t = −2.07, df = 1, 105, p = 0.04)], and higher body mass index (BMI) was associated with better immediate (beta =0.21, t = 2.41, df = 1,105, p = 0.02) and delayed (beta = 0.22, t = 2.46, df = 1,105, p = 0.02) verbal memory performance following adjustment for age, education, and psychiatric disorders. There was an inverse correlation between SHBG levels and BMI (Pearson's r = −0.37, n = 112, p <0.001). Estimated free testosterone levels revealed curvilinear associations with verbal memory performance
Xing 2013[47]	Compared to controls, the testosterone and SHBG levels were lower in

	male VaD patients, and the estradiol levels were higher in female VaD patients. The hormones levels were not correlated with cognitive functions among either male or female VaD patients. There were no associations between hormone levels and neuropsychiatric symptoms among male patients, while the TE2 and TT levels were positively associated with apathy and anxiety, respectively among female patients. Sex hormones were associated with neuropsychiatric symptoms among female but not male VaD patients
Yaffe 2002[48]	No consistent association between total testosterone level and cognitive test scores was observed. However, men with high bioavailable (loosely proteinbound) testosterone had better cognitive test scores on all three tests (P<=.001). Total estradiol levels were associated with worse cognitive scores on Digit Symbol (P<.001) and Trails B (P=.002), but bioavailable estradiol levels were not associated with cognitive function. Level of sex hormone binding globulin (SHBG) was negatively associated with cognitive scores on all three tests (P<=.001). After adjusting for age and education, the statistical significance lessened for bioavailable testosterone (MMSE, P=.086; Digit Symbol, P =.047; Trails B, P= .076) and became nonsignificant for SHBG (all cognitive tests P>.10).
Yaffe 2007[49]	Women in the lowest estradiol tertile were more likely than those in the highest tertile to decline (≥1.0 S.D. of change) on 3MS (25% versus

9%, adjusted odds ratio [OR] = 3.9; 95% confidence interval [CI] = 1.6–9.6) and on SRT (28% versus 12%, adjusted OR [95% CI] = 3.3 [1.4–7.9]) but not CLOX 1. There was a borderline association between low estradiol tertile and decline on SRT in men (22% versus 14%, adjusted OR [95% CI] = 1.9 [0.9–3.9]). Testosterone level was not associated with decline in cognition in either men or women. Findings did not differ by race.