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Androgens In Men Study (AIMS): protocol for meta-analyses of individual participant data investigating associations of androgens with health outcomes in men.

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Complete List of Authors:	<p>Yeap, Bu; University of Western Australia, Medical School; Fiona Stanley Hospital, Department of Endocrinology and Diabetes Marriott, Ross; University of Western Australia, School of Population and Global Health Adams, Robert; Flinders University, Adelaide Institute for Sleep Health Antonio, Leen; KU Leuven, Clinical and Experimental Endocrinology Ballantyne, Christie; Baylor College of Medicine, Internal Medicine Bhasin, Shalender; Harvard Medical School Cawthon, PM; California Pacific Medical Center Research Institute, San Francisco Coordinating Center Couper, David; University of North Carolina at Chapel Hill, Gillings School of Global Public Health Dobs, Adrian; Johns Hopkins University, School of Medicine, Division of Endocrinology, Diabetes and Metabolism Flicker, Leon; University of Western Australia, WA Centre for Health & Ageing Karlsson, Magnus; Lund University, Department of Clinical Sciences and Orthopedic Surgery Martin, Sean A.; The University of Adelaide, Freemasons Foundation Centre for Men's Health Matsumoto, AM; VA Puget Sound Health Care System, Geriatric Research, Education and Clinical Center; University of Washington System, Medicine Mellström, Dan ; University of Gothenburg, Centre for Bone and Arthritis Research at the Sahlgrenska Academy, Institute of Medicine Norman, Paul; University of Western Australia, Medical School Ohlsson , C; University of Gothenburg, Centre for Bone and Arthritis Research at the Sahlgrenska Academy, Institute of Medicine Orwoll, Eric; Oregon Health & Science University O'Neill, Terence; The University of Manchester & NIHR Manchester Biomedical Research Centre, Centre for Epidemiology Versus Arthritis, Faculty of Biology, Medicine and Health; Manchester Academic Health Science Centre, Manchester University NHS Foundation Trust Shores, Molly; VA Puget Sound Health Care System; University of Washington, School of Medicine, Department of Psychiatry and Behavioral Sciences Travison, Thomas; Beth Israel Deaconess Medical Center, Institute for Aging Research, Hebrew SeniorLife; Harvard Medical School Vanderschueren, Dirk; Katholieke Universiteit Leuven, Department of</p>

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	Chronic Diseases, Metabolism and Ageing (CHROMETA), Laboratory of Clinical and Experimental Endocrinology Wittert, Gary; The University of Adelaide, Freemasons Centre for Men's Health Wu, Frederick; The University of Manchester, Division of Diabetes, Endocrinology and Gastroenterology Murray, Kevin; University of Western Australia, School of Population and Global Health
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3 1 Androgens In Men Study (AIMS): protocol for meta-analyses of individual participant data
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5 2 investigating associations of androgens with health outcomes in men.
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9
10 4 Corresponding author

11
12 5 Dr Bu B. Yeap MBBS, FRACP, PhD, Harry Perkins Institute of Medical Research, 11 Robin
13
14 6 Warren Drive, Murdoch 6150, Western Australia, Australia.

15
16
17 7 Email: bu.yeap@uwa.edu.au; Telephone: +61 8 6151 1149
18
19 8

20
21 9 Authors:

22
23
24 10 Bu B. Yeap, Medical School, The University of Western Australia, Perth 6009, Australia.

25
26 11 Ross J. Marriott, School of Population and Global Health, The University of Western
27
28 12 Australia, Perth 6009, Australia.

29
30 13 Robert J. Adams, Adelaide Institute for Sleep Health, Flinders University, Bedford Park
31
32 14 5042, Australia.

33
34
35 15 Leen Antonio, Clinical and Experimental Endocrinology, KU Leuven, Leuven, Belgium.

36
37 16 Christie M. Ballantyne, Internal Medicine, Baylor College of Medicine, Houston, Texas,
38
39 17 USA.

40
41
42 18 Shalender Bhasin, Harvard Medical School, Boston, Massachusetts, USA.

43
44 19 Peggy M. Cawthon, San Francisco Coordinating Center, California Pacific Medical Center
45
46 20 Research Institute, San Francisco, California, USA.

47
48
49 21 David J. Couper, Gillings School of Global Public Health, University of North Carolina at
50
51 22 Chapel Hill, Chapel Hill, North Carolina, USA.

52
53
54 23 Adrian S. Dobs, School of Medicine, Division of Endocrinology, Diabetes and Metabolism,
55
56 24 Johns Hopkins University, Baltimore, Maryland, USA.
57
58
59
60

- 1
2
3 25 Leon Flicker, WA Centre for Health & Ageing, The University of Western Australia, Perth
4
5 26 6009, Australia.
6
7 27 Magnus Karlsson, Department of Clinical Sciences and Orthopedic Surgery, Lund
8
9 28 University, Lund, Sweden.
10
11
12 29 Sean A. Martin, Freemasons Foundation Centre for Men's Health, The University of
13
14 30 Adelaide, Adelaide 5000, Australia.
15
16 31 Alvin M. Matsumoto, Geriatric Research, Education and Clinical Center, VA Puget Sound
17
18 32 Health Care System, Seattle, Washington, USA.
19
20 21 33 Dan Mellström, Centre for Bone and Arthritis Research at the Sahlgrenska Academy,
22
23 34 Institute of Medicine, University of Gothenburg, Goteburg, Sweden.
24
25 26 35 Paul E. Norman, Medical School, The University of Western Australia, Fremantle 6160,
27
28 36 Australia.
29
30 31 37 Claes Ohlsson, Centre for Bone and Arthritis Research at the Sahlgrenska Academy, Institute
32
33 38 of Medicine, University of Gothenburg, Goteburg, Sweden.
34
35 39 Eric S. Orwoll, Oregon Health & Science University, Portland, Oregon, USA.
36
37 40 Terence W. O'Neill, Centre for Epidemiology Versus Arthritis, Faculty of Biology, Medicine
38
39 41 and Health, The University of Manchester & NIHR Biomedical Research Centre,
40
41 42 Manchester, United Kingdom.
42
43 44 43 Molly M. Shores, VA Puget Sound Health Care System, Seattle, Washington, United States.
44
45 46 44 Thomas G. Travison, Institute for Aging Research, Hebrew SeniorLife, Beth Israel
47
48 45 Deaconess Medical Center, Boston, Massachusetts, USA.
49
50 51 46 Dirk Vanderschueren, Department of Chronic Diseases, Metabolism and Ageing
52
53 47 (CHROMETA), Laboratory of Clinical and Experimental Endocrinology, Katholieke
54
55 48 Universiteit Leuven, Leuven, Flanders, Belgium.
56
57
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60

1
2
3 49 Gary A. Wittert, Freemasons Foundation Centre for Men's Health, The University of
4
5 50 Adelaide, Adelaide 5000, Australia.
6
7 51 Frederick C. W. Wu., Division of Diabetes, Endocrinology and Gastroenterology, The
8
9 52 University of Manchester, Manchester, United Kingdom.
10
11
12 53 Kevin Murray, School of Population and Global Health, The University of Western Australia,
13
14 54 Perth 6009, Australia.
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62 **ABSTRACT**

63 **Introduction**

64 This study aims to clarify the role(s) of endogenous sex hormones to influence health
65 outcomes in men, specifically to define the associations of plasma testosterone with incidence
66 of cardiovascular events, cancer, dementia and mortality risk, and to identify factors
67 predicting testosterone concentrations. Data will be accrued from at least three Australian,
68 two European, and four North American population-based cohorts involving approximately
69 20,000 men.

70 **Methods and analysis**

71 Eligible studies include prospective cohort studies with baseline testosterone concentrations
72 measured using mass spectrometry and five years of follow-up data on incident
73 cardiovascular events, mortality, cancer diagnoses or deaths, new onset dementia, or decline
74 in cognitive function recorded. Data for men, who were not taking androgens or drugs
75 suppressing testosterone production, metabolism, or action; and had no prior orchidectomy,
76 are eligible. The date range of bibliographic searches will not be constrained, and aggregate
77 level data will be sought where individual participant data (IPD) is not available. One-stage
78 IPD random-effects meta-analyses will be performed, using linear mixed models, generalised
79 linear mixed models and either stratified or frailty-augmented Cox regression models.
80 Heterogeneity in estimates from different studies will be quantified and bias investigated
81 using funnel plots. Effect size estimates will be presented in forest plots and non-negligible
82 heterogeneity and bias investigated using subgroup or meta-regression analyses.

83 **Ethics and dissemination**

84 Ethics approvals obtained for each of the participating cohorts state that participants have
85 consented to have their data collected and used for research purposes. There are four planned
86 research articles, with each involving a separate set of IPD meta-analyses.

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3 87 **Registration** [Systematic Review Protocol ID 139668 submitted to Prospero on 23 July 2019
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5 88 and is presently being assessed].
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10 90 **STRENGTHS AND LIMITATIONS OF THIS STUDY**
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- 12 91 • A large international collaboration combining data from multiple cohorts will enable
13
14 92 definitive analyses whose results possess global applicability. Investigators from at least
15
16 93 three large Australian, two European, and four North American cohorts (each with N >
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18 94 1,000 participants), which have IPD-level data available, have agreed to collaborate and
19
20 95 confirmed availability of suitable IPD-level data, provisional on approvals from their
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22 96 local IRBs. Aggregate level data will be sought in the event IPD-level data are not
23
24 97 available.
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26 98 • Harmonization will be required for some variables (e.g., physical activity, alcohol
27
28 99 consumption) that are recorded differently by the component studies.
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31 100 • Analyses will allow reference ranges for testosterone in men across ages and geographical
32
33 101 locations to be refined to inform recommendations for clinical practice.
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103 INTRODUCTION

104 As men grow older, testosterone production and circulating concentrations of testosterone
105 decline while comorbidities accumulate.[1-4] Older men, even those in very good health,
106 have lower circulating testosterone concentrations compared with healthy young men.[5, 6]
107 Although results have been inconsistent, an increasing number of studies have reported
108 associations of low endogenous testosterone concentration with poorer health outcomes,
109 especially in older men. For instance, studies that have used liquid chromatography tandem
110 mass spectrometry, widely regarded as the reference method for the measurement of total
111 testosterone concentrations,[7] have reported associations of lower endogenous testosterone
112 concentrations with: (i) cardiovascular disease and all-cause mortality in some cases[8-15]
113 but not others[8, 16-20]; (ii) some cancers but not others[21, 22]; and (iii) dementia[23, 24]
114 but not laboratory measures of cognitive function.[25] Therefore it remains unclear whether
115 testosterone is a biomarker of ill-health or a causal factor for diseases of ageing.
116
117 Currently, testosterone treatment is recommended for men who have symptoms and signs of
118 androgen deficiency and low testosterone concentrations, due to disease of the hypothalamus,
119 pituitary or testes (organic or pathological hypogonadism).[26-29] Randomised controlled
120 trials of testosterone treatment in older men with low-normal testosterone concentrations
121 without organic hypogonadism have shown modest benefits on sexual function, anaemia,
122 self-reported physical function and mobility, and volumetric bone density, but not on some
123 objective measures of cognition over 12 to 36 months.[30-34] The effect of testosterone on
124 major adverse cardiovascular events remains unclear.[35, 36] However, the selection criteria
125 of these trials was such that the screening to enrolment ratio was 65:1, a highly selected
126 population of older men.[32, 33, 36] Importantly, the trials were neither large enough nor
127 long enough to determine the effects of testosterone on major adverse cardiovascular events,

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3 128 development of dementia, bone fractures, and mortality.[36] Therefore, a meta-analysis of
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5 129 data from prospective cohort studies, with extended follow-up periods, provides opportunities
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8 130 for better understanding of the temporal profiles of the postulated associations between
9
10 131 endogenous testosterone concentration and incident health outcomes. Meta-analyses of
11
12 132 Individual Participant Data (IPD) are generally preferable to meta-analyses of aggregate data
13
14 133 in that they typically have higher statistical power and provide scope to control for important
15
16
17 134 confounders and risk factors.[37, 38] Furthermore, one-stage IPD meta-analyses are
18
19 135 preferable to two-stage approaches because the former uses an exact likelihood to directly
20
21 136 model the distribution of IPD, offers the convenience of using a standard set of diagnostic
22
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24 137 tools to assess model fit, and can arguably provide greater flexibility, in terms of options for
25
26 138 statistical modelling.[39, 40]

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31 140 The Androgens In Men Study (AIMS), an international collaboration of prospective cohort
32
33 141 studies, will examine the associations of sex hormones with health outcomes that are major
34
35 142 sources of morbidity and mortality in middle-aged and older men. The group will perform a
36
37 143 series of IPD meta-analyses to clarify the influence of sex hormone exposures on major
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40 144 health outcomes, including heart attack, stroke and cardiovascular deaths, cancer, new-onset
41
42 145 dementia, and all-cause mortality, as well as provide information on social, demographic and
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44 146 behavioural factors that are associated with endogenous testosterone concentrations. This
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47 147 work will characterise robustly the associations of androgens with health outcomes in men in
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49 148 general over and above the study-specific estimates, thus clarifying the role of androgens as
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51 149 biomarkers for, or causal contributors to, men's health.

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3 **151 Objectives**
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5 152 The Androgens In Men Study (AIMS) will establish an international collaboration of existing
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7 153 cohort studies to clarify the relation of endogenous sex hormones with major health outcomes
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10 154 in men. PEO (Population, Exposure, Outcomes) characteristics include: adult men in the
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12 155 general community; an exposure of endogenous circulating sex hormone concentration,
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14 156 primarily testosterone, as the principal male sex hormone or androgen; and a prospective
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17 157 cohort study type, with incident health outcomes including incidence of cardiovascular
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19 158 disease events, mortality, cancers, and dementia. The specific objectives of the AIMS study
20
21 159 are: to investigate associations between variables representing social, demographic, and
22
23 160 behavioural factors with the measured concentration of androgens in the blood of men
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25
26 161 (Analysis 1); to examine the associations between androgen concentrations and subsequent
27
28 162 incidence of cardiovascular events, cardiovascular deaths, and all-cause mortality in men
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30 163 (Analysis 2); to examine the associations between androgen concentrations and subsequent
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32 164 mortality from (and, if available, diagnoses of) common cancers in men (Analysis 3); to
33
34 165 examine the associations between androgen concentrations and cognitive impairment and
35
36 166 incident dementia in men (Analysis 4). Analysis 2 will evaluate myocardial infarction, stroke
37
38 167 and heart failure, deaths due to cardiovascular disease, and the composite endpoint of major
39
40 168 adverse cardiovascular events (MACE) comprising non-fatal myocardial infarction, non-fatal
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42 169 stroke, and deaths due to cardiovascular disease. Analysis 3 will evaluate outcomes of deaths
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44 170 due to and diagnoses of colorectal cancer, lung cancer and prostate cancer.
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172 **METHODS AND ANALYSIS**

173 IPD meta-analyses will be conducted to understand the associations between testosterone and
174 a range of associated major health outcomes in men. IPD meta-analyses have been selected
175 as the most suitable approach because: (i) the required aggregate data (AD) are not available
176 from each of the cohorts in published literature; (ii) IPD meta-analyses typically have higher
177 statistical power than AD meta-analyses and provide scope for controlling for important
178 confounders and risk factors.[37, 38] Where possible, methods will adhere to the guidelines
179 for Preferred Reporting Items for Systematic Reviews and Meta-Analyses of IPD data
180 (PRISMA-IPD; completed checklist is provided in Supplementary Material) and the Meta-
181 analysis Of Observational Studies in Epidemiology (MOOSE).[41-43]

182

183 **Studies selected for inclusion in IPD meta-analyses**

184 Studies will be identified from a systematic review using online search tools for mainstream
185 published (MEDLINE, EMBASE) and grey literature (OpenGrey, Mednar) studies (Prospero
186 application for registration No. 139668 submitted 23 July 2019). Eligible studies include
187 prospective cohort studies with plasma or serum testosterone concentrations measured using
188 mass spectrometry with at least five years of follow-up data, with incident cardiovascular,
189 cancer, mortality, dementia, or cognitive events recorded (see Supplementary Table S1 for an
190 example of search criteria to be used). The search strategy selects for articles based on words
191 or Medical Subject Headings (MeSH) terms matching the relevant exposure (example steps
192 1-3), outcomes (example steps 4-10), and study type (example steps 14-15), then, depending
193 on the search tool, filters down to more relevant studies, with exclusions of clinical trials and
194 of studies on non-humans (example steps 18-27), with no date range restrictions. Ahead of
195 the systematic review, nine eligible studies (cohorts) had expressed interest to collaborate:
196 three from Australia (Busselton Health Study BHS, Health In Men Study HIMS, Men

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3 197 Androgen Inflammation Lifestyle Environment and Stress study MAILES); two from Europe
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5 198 (European Male Ageing Study EMAS, Osteoporotic Fractures in Men Study MrOS -
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8 199 Sweden); and four from the USA (Atherosclerosis Risk in Communities study ARIC,
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10 200 Cardiovascular Health Study CHS, The Framingham Heart Study FHS, Osteoporotic
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12 201 Fractures in Men Study MrOS - USA). Investigators from eight of these studies have
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14 202 confirmed availability of suitable IPD-level data, provisional on approvals from their
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17 203 respective Publication and Steering Committees. If it is not possible to obtain IPD-level data
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19 204 from selected studies, we will request suitable AD-level data.
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23 24 206 **Data provision, merging, harmonisation, and storage**

25
26 207 The project manager will liaise directly with the nominated contact person for each cohort
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28 208 study to identify, specifically, which variables and set of observations will be suitable to
29
30 209 request. A data request will then be submitted to the data custodian for each study. Requested
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33 210 variables will be labelled as either “highly desirable” or “only if available”, in order to
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35 211 prioritise efforts in obtaining the key variables for analyses and to acknowledge the differing
36
37 212 availability of variables among studies. A list of variable names, definitions, and attributes,
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39 213 including numbers of rows and columns in each data file(s) will also be requested to be
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41
42 214 provided separately. Methods for ascertaining outcome and comorbidity status will be
43
44 215 requested, which can be used to indicate the relative quality of diagnostic information (e.g.
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46 216 ICD-coded diagnoses from hospital inpatient admissions versus self-report information). File
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48 217 transfer will be achieved via encrypted file transfer (or other sufficiently secure method).
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53 219 Once each dataset has been received by the project manager, the original file(s) will be saved
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55 220 and date-stamped in a secure central repository. All subsequent manipulations will be
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57 221 completed using copies of the original file, with syntax saved as script files. Variable
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3 222 definitions will be checked, variables inspected for missing values, and variable properties
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5 223 and value ranges assessed to identify possible outliers. A table of summary statistics will be
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8 224 calculated and, where possible, analyses run and compared with published values to check for
9
10 225 data consistency. The nature of any discrepancies identified from these checks will need to be
11
12 226 understood, and possibly resolved, prior to proceeding with the meta-analyses.[42, 44, 45]
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14 227 Missing data will be suitably imputed.[45, 46]
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20 229 Prior to the merging of datasets, a variable to identify each source study will be appended as
21
22 230 the new first column. Variable formats will be checked and corrected for consistency and
23
24 231 anonymised participant identifier codes for uniqueness across all studies. Harmonization will
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26 232 be required for some variables (e.g., physical activity, alcohol consumption) that are recorded
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28 233 differently by the different component studies. Where possible, AD datasets will be used to
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30 234 reconstruct IPD-level data (that is, partially-reconstructed IPD) prior to merging.[47-49]
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33 235 Should this not be possible, the IPD-level data will be aggregated and summary estimates
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35 236 made with and without AD-level data as sensitivity analyses. It is also possible that some
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37 237 studies might have outcomes available for some analyses, but not others; in these cases, we
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39 238 will preferentially use IPD-level data when available but also seek to use AD-level data from
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41 239 those other studies when available. There is no requirement to use IPD-level data from the
42
43 240 same studies across all analyses.
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49 242 All IPD-level data will be accessible to only the approved staff from a secure on-site facility,
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51 243 from rooms that are kept locked when unattended, and with remote access not permitted.
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53 244 IPD-level data are not to be printed in hard copy and will only be presented at aggregate
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55 245 level. Data analysed for this study will be retained for five years after the last of all proposed
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57 246 analyses are published and will then be destroyed. A post-analysis retention period is required
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3 247 to enable publication and possible scrutiny of findings. Disposal will be carried out according
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5 248 to best practice.
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10 11 250 **Data items**

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14 251 The full list of generic variables to include in meta-analyses are presented in Table 1.

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16 252 Analysis 1 will model relationships of androgen concentrations, as measured in serum or
17
18 253 plasma samples (dependent variable), with key demographic variables and risk factors for
19
20 254 disease (predictor variables). Time-to-event variables obtained from follow-up data will be
21
22 255 analysed in Analysis 2 and 3 (outcomes), and their associations with androgen concentrations
23
24 256 (focal predictor) and other potential confounders and risk factors (predictor variables).
25
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28 257 Records of dementia diagnoses (physician or otherwise categorised) and relative cognitive
29
30 258 function (for example, from test scores) will be analysed in Analysis 4, and their associations
31
32 259 with androgen concentrations and other potential confounders and risk factors. Androgen
33
34 260 variables will include measurements of total testosterone and, if available, of
35
36 261 dihydrotestosterone, estradiol, luteinising hormone (LH), and Sex Hormone Binding Globulin
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38 262 (SHBG). For exploratory analyses, free testosterone, the amount in the circulation which is
39
40 263 not protein-bound, will be calculated from measured total testosterone and SHBG.[50]
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44 264 Covariates were selected to include those used in previous studies, as well as those that are
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46 265 typically recorded. The full list of proposed variables to include in the meta-analyses are
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48 266 presented in Table 1.
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53 54 268 **Statistical analysis**

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56 269 Since the datasets to be analysed are sampled from different populations, a random-effects
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58 270 meta-analysis is appropriate, as it acknowledges that effects will vary among studies due to
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3 271 differences in local factors.[51] One-stage IPD meta-analyses will be performed. Each IPD
4
5 272 meta-analysis will involve fitting a model with study estimated as either a fixed or random
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7 273 term, to account for related observations within studies, and androgen modelled as random
8
9 274 slopes (when modelled as a continuous predictor) or intercepts (when modelled as a
10
11 275 categorical predictor), to harmonised, merged data from all cohorts. The underlying statistical
12
13 276 model and estimates of effect size will be specific to each of the proposed analyses and are
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15 277 outlined as follows.
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23 279 *Analysis 1: Factors associated with testosterone concentrations in men and characterisation*
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25 280 *of reference ranges.*
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28 281 Linear Mixed Models (LMMs) or Generalised Linear Mixed Models (GLMMs) will be used
29
30 282 to model the relation between the predictors (independent variables) and each hormonal
31
32 283 variable (testosterone, dihydrotestosterone, estradiol, LH, SHBG) as five separate IPD meta-
33
34 284 analyses. Suspected non-linear relationships, at the scale of the linear predictor, will be
35
36 285 investigated and modelled appropriately (e.g., splines with pre-set knot locations and linear
37
38 286 boundary constraints). Measures of effect size may include (but are not limited to): η^2 , [52,
39
40 287 53] Pearson's r , standardised mean difference to the reference level (categorical predictors),
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42 288 standardised difference for an increase in one standard deviation (continuous predictors). In
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44 289 the case of non-linear relations, we will graphically describe the relationship with
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46 290 comparisons made with appropriate reference points. Reference ranges will be derived based
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48 291 on the distributions of testosterone in healthy men.
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3 293 *Analysis 2: Associations between testosterone concentrations and subsequent incidence of*
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5 294 *cardiovascular events, cardiovascular deaths, and all-cause mortality.*

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8 295 Cox proportional hazards models will be used to assess the effect of androgen level on the
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10 296 incident risk of each outcome, with separate IPD meta-analyses conducted for each outcome
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12 297 (myocardial infarction, stroke, heart failure, deaths due to cardiovascular disease, and
13
14 298 MACE) and each hormonal variable (testosterone, dihydrotestosterone, estradiol, LH,
15
16 299 SHBG). Component study will be modelled either as a stratified variable[39] or as a random
17
18 300 term, and androgen as a random term, using frailty models, which are a class of survival
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20 301 models that incorporate random effects.[54-56] Participants with prevalent cardiovascular
21
22 302 disease at baseline will be excluded. The length of follow-up will also be standardised among
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24 303 studies in order to maximise data from all datasets, whilst minimising the prospect for
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26 304 variable lengths-to-follow-up among studies introducing additional heterogeneity into
27
28 305 results.[46]

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37 307 Multivariable versions of each of these models will also be fitted, with additional predictors
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39 308 for potential confounders and risk factors included (Table 1). Non-linear associations for
40
41 309 continuous variables will be modelled using natural splines with pre-specified knots and
42
43 310 linear boundary constraints. The (standardised) measure of effect size used will be the hazard
44
45 311 ratio. Subgroup analyses will be conducted separately for each of three specific types of
46
47 312 cardiovascular disease (outcomes): myocardial infarction, stroke and heart failure.

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53 314 *Analysis 3: Association between testosterone level and subsequent incidence of cancer.*

54
55 315 Cox proportional hazards models will be used to assess the effect of androgen concentrations
56
57 316 on the incident risk of cancer deaths and, if available, of cancer diagnoses. IPD meta-analyses
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3 317 separately conducted for each of these outcomes and each hormonal variable as focal
4
5 318 predictor (testosterone, dihydrotestosterone, estradiol, LH, SHBG). Component study will be
6
7 319 modelled either as a stratified variable[39] or as a random term, and androgen as a random
8
9 320 term, using frailty models.[54-56] Participants with prevalent cancer diagnosis at baseline
10
11 321 will be excluded. The length of follow-up will be standardised among studies in order to
12
13 322 maximise data from all datasets, whilst minimising the prospect for variable lengths-to-
14
15 323 follow-up among studies introducing additional heterogeneity into results.[46]
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22 325 Multivariable versions of each of these models will also be fitted, with additional predictors
23
24 326 for potential confounders and risk factors included (Table 1). Non-linear associations for
25
26 327 continuous variables will be modelled using natural splines with pre-specified knots and
27
28 328 linear boundary constraints. The (standardised) measure of effect size used will be the hazard
29
30 329 ratio. Subgroup analyses will be conducted separately for each of three common types of
31
32 330 cancers in men (outcomes): colorectal cancer, lung cancer, prostate cancer. For these
33
34 331 analyses, men with the relevant cancer type at baseline will be excluded from that specific
35
36 332 analysis. Thus men with prevalent colorectal cancer (but not other cancer types) will be
37
38 333 excluded in the analysis of incident colorectal cancer; similarly for the analyses of incident
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40 334 lung and prostate cancer, men with lung or prostate cancer at baseline will be excluded.
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48 336 *Analysis 4: Associations of androgen levels with cognitive impairment and incident dementia*
49
50 337 *in men.*

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52 338 LMMs and GLMMs will be used to model the association of androgen concentrations with
53
54 339 cognitive impairment (cross-sectional analyses of baseline data). Cox proportional hazards
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56 340 models will be used to assess the effect of androgen concentrations on the incident risk of
57
58 341 dementia. Men with prevalent dementia will be excluded from this analysis. We will also ask
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3 342 for follow-up cognition test scores, and if available, will run an analysis of changes in
4
5 343 cognition test scores from baseline as an outcome. Separate IPD meta-analyses will be
6
7 344 conducted for each hormonal variable as a focal predictor (testosterone, dihydrotestosterone,
8
9 345 estradiol, LH, SHBG). Component study will be modelled as a fixed or random intercept
10
11 346 term in LMMs and GLMMs and as a stratified factor or frailty model random term in Cox
12
13 347 regressions. Multivariable versions of each of these models will also be fitted, with additional
14
15 348 predictors for potential confounders and risk factors included (Table 1). Suspected non-linear
16
17 349 relationships, at the scale of the linear predictor, will be investigated and modelled using
18
19 350 splines with pre-specified knots and boundary constraints. Measures of effect size may
20
21 351 include: η^2 , Pearson's r , standardised mean difference to the reference level (categorical
22
23 352 predictors), standardised difference for an increase in one standard deviation (continuous
24
25 353 predictors), odds ratio for LMMs and GLMMs and hazard ratio for Cox regressions.
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33 355 Throughout all analyses, contour-enhanced funnel plots will be constructed to visually assess
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35 356 patterns in estimates of effect sizes and precision among studies, to investigate heterogeneity
36
37 357 and possible meta-biases.[57-59] The relative amount of heterogeneity will be estimated
38
39 358 (e.g., using I^2) and forest plots presented. Subgroup or meta-regression analyses may be
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41 359 conducted if pronounced heterogeneity is estimated.[51]
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47 361 **Patient and public involvement**

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49 362 The level and type of participant/patient and public involvement will pertain to each
50
51 363 respective component study used for the meta-analyses, with additional studies to be
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53 364 identified from systematic review. Accordingly, we refer the reader to respective published
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55 365 journal articles for each component study for further details.[60-67]
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367 **ETHICS AND DISSEMINATION**

368 Ethics approvals obtained for each of the participating cohorts state that participants have
369 consented to have their data collected and used for research purposes. Furthermore, there are
370 no expected harms or risks to participants, as data have already been collected within each
371 individual cohort, under existing ethics approvals. De-identified data will be collated and
372 analysed, with no new procedures planned for participants. The AIMS study has been
373 assessed as exempt from ethics review by the Human Research Ethics Office at the
374 University of Western Australia (file reference number RA/4/20/5014).

375

376 **DISCUSSION**

377 Although several published meta-analyses have investigated associations of endogenous
378 testosterone with health outcomes in men,[68-79] none have conducted IPD meta-analyses of
379 health outcomes as planned for this study. A previous IPD meta-analysis focussed on the
380 outcome of metabolic syndrome.[71] Results from this study will improve upon previously
381 published estimates from individual studies, in terms of the generalisability of findings.
382 Estimates from the IPD meta-analyses are also likely to be more reliable than those published
383 from conventional meta-analyses because they typically have higher statistical power and
384 provide scope for controlling for important confounders and risk factors.[37, 38] Uncertainty
385 will undoubtedly remain due to the possibility of confounding influences of unadjusted
386 effects. However, unlike a randomised controlled trial, this study avoids the need to subject
387 individuals to interventions, and provides more comprehensive characterisation of temporal
388 relationships between baseline androgen concentrations and a range of key health
389 outcomes.[80]

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3 391 Accordingly, it is hoped that the AIMS collaboration will ultimately complement the research
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5 392 efforts and outputs from multiple prospective cohort studies by drawing upon the collective
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7 393 body of evidence to clarify the role of endogenous sex hormone levels on major health
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9 394 outcomes in men. It is possible that this work might also elucidate new understanding, arising
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11 395 from improved scope for fitting more complex models due to increased statistical power, or
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13 396 from patterns detected in subgroup or meta-regression analyses. Clinically, research outputs
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15 397 will be used to identify the scope and optimal recruitment criteria for future trials of
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17 398 testosterone therapy. These data will also allow reference ranges for testosterone in men
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19 399 across ages and geographical locations to be refined, to inform recommendations for clinical
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21 400 practice more generally.
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30 402 **CONCLUSION**

31 403 This new collaboration (the AIMS study) and series of IPD-meta analyses described here will
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33 404 complement previous research efforts and outputs from a number of prospective cohort
34
35 405 studies for describing associations between endogenous androgen concentrations and health
36
37 406 outcomes in men. Research outputs will serve to progress the collective body of knowledge
38
39 407 and clarify the importance of testosterone for male health more generally, with several key
40
41 408 implications for clinical practice, including prevention (of testosterone decline), personalised
42
43 409 medicine and testosterone therapy.
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6
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13 420 **Collaborators**

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15 421 The Androgens In Men Study: (1) Busselton Health Study: Busselton Population Medical
16
17 422 Research Institute (Inc.), Department of Pulmonary Physiology and Sleep Medicine, Sir
18
19 423 Charles Gairdner Hospital, Nedlands WA 6009, Australia (2) Health In Men Study (HIMS):
20
21 424 Western Australian Centre for Health and Ageing, University of Western Australia, Level 6
22
23 425 Medical Research Foundation Building, Royal Perth Hospital, Rear 50 Murray Street, Perth,
24
25 426 Western Australia 6000, Australia. (3) Men Androgen Inflammation Lifestyle Environment
26
27 427 and Stress (MAILES) study: Freemasons Foundation Centre for Men's Health, University of
28
29 428 Adelaide, 254 North Tce, Adelaide, Australia. (4) European Male Ageing Study (EMAS):
30
31 429 The University of Manchester, Stopford Building, Oxford Road, Manchester, M13 9PT, UK.
32
33 430 (5) Osteoporotic Fractures in Men (MrOS) Study Sweden: Department of Clinical Sciences
34
35 431 and Orthopedic Surgery, Lund University, Skåne University Hospital, Malmö, Sweden;
36
37 432 MrOS Study USA: California Pacific Medical Center Research Institute, San Francisco
38
39 433 Coordinating Center, 550 16th street, San Francisco, CA 94143. (6) Atherosclerosis Risk in
40
41 434 Communities study (ARIC): School of Public Health, U. of North Carolina, Suite 2013,
42
43 435 NCNB Plaza, 137 E. Franklin St, Chapel Hill, NC 27514. (7) Cardiovascular Health Study:
44
45 436 National Heart, Lung, and Blood Institute, Bethesda, MD. (8) The Framingham Heart Study,
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47 437 Boston University School of Medicine, 72 E. Concord Street, B-601, Boston, MA 02118.
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3 439 **Authors' contributions**
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5 440 BBY, KM, LA, SB, ASD, AMM, CO, EO, TWO, DV, GAW, contributed to the study
6
7 441 concept and design. BBY, KM, RJM prepared the initial draft of the manuscript, including
8
9 442 literature review, list of variables and statistical methods. All authors were involved in
10
11 443 subsequent revisions to the protocol and manuscript, and approved this submission.
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487
488 **Competing interests**

489 None declared.

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5 491 **Patient consent**

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8 492 Each of the component studies have addressed participant/patient consent permissions; please
9
10 493 refer to respective component studies for details.[60-67]
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15 495 **Ethics approval**

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17 496 The AIMS study has been assessed as exempt from ethics review by the Human Ethics office
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19 497 at the University of Western Australia (file reference number RA/4/20/5014). Each of the
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21 498 component studies had obtained ethics approvals; please refer to respective component
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23 499 studies for details.[60-67]
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713 TABLES

714 Table 1. Variables planned to be included in IPD meta-analysis modelling.¶¶

Type	Analysis 1	Analysis 2	Analysis 3	Analysis 4
Outcomes / DV	Androgen concentration§	Incident CVD*	Incident deaths (cancer*)	Incident dementia
		Incident deaths (CVD*)	Incident cancer* (diagnoses)	Baseline cognition
		Incident deaths (all-cause)		Change in cognition
Focal predictor	-	Androgen concentration§	Androgen concentration§	Androgen concentration§
Covariates / IV				
Demographic	age	age	age	age
	education level	education level	education level	education level
	ethnicity	ethnicity	ethnicity	ethnicity
	marital status	marital status	marital status	marital status
	site	site	site	site
Risk factors and comorbidities	alcohol consumption	alcohol consumption	alcohol consumption	alcohol consumption
	BMI, waist	BMI, waist	BMI, waist	BMI, waist
	physical activity	physical activity	physical activity	physical activity
	smoking status	smoking status	smoking status	smoking status
	BP, hypertension	BP, hypertension	BP, hypertension	BP, hypertension
	general health	general health atrial fibrillation	general health	general health
	prevalent CVD	prevalent CVD		
	prevalent cancer*		prevalent cancer*	
	prevalent dementia			prevalent dementia
	baseline cognition			
	COPD	COPD		
	diabetes	diabetes	diabetes	diabetes
	cholesterol, LDL, HDL	cholesterol, LDL, HDL		
	creatinine level	creatinine level		
	lipid lowering medications	lipid lowering medications		
	anxiety			anxiety
	depression			depression
	psychotropic drug use			psychotropic drug use

715 **Abbreviations:** BMI = body mass index; BP= blood pressure; CVD = Cardiovascular
716 Disease; DV = dependent variable; COPD = Chronic Obstructive Pulmonary Disease;
717 IV = independent variables.

718 ¶¶ = Black font: highly desirable; Green font: only if available.

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719 § = Androgens: total testosterone, dihydrotestosterone, estradiol, luteinising hormone, sex
720 hormone binding globulin.
721 * = Subgroup analyses are also planned. For CVD outcomes: Heart Failure, Myocardial
722 Infarction, Stroke. For cancer outcomes: colorectal cancer, lung cancer, prostate
723 cancer.

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Supplementary Table S1. Example search strategy for systematic review: AIMS study.

The following is an example of a preliminary search conducted in MEDLINE.

1. Testosterone/ or Androgens/
2. (testosterone or androgen* or sex hormone* or sex steroid*).ti.
3. (testosterone or androgen*).ab.
4. cardiovascular diseases/ or heart diseases/ or heart failure/ or vascular diseases/ or stroke/ or myocardial infarction/ or coronary disease/ or cerebrovascular disorders/
5. (cardiovascular or stroke or myocardial infarction or heart failure).ti.
6. neoplasms/ or colorectal neoplasms/ or lung neoplasms/ or prostatic neoplasms/
7. cancer.ti.
8. mortality/ or mortality.ti.
9. dementia/ or cognition/ or dementia.ti. or cognit*.ti.
10. Aging/psychology or Neuropsychological Tests/
11. 1 or 2 or 3
12. 4 or 5 or 6 or 7 or 8 or 9 or 10
13. 11 and 12
14. longitudinal studies/ or prospective studies/ or follow-up studies/ or cohort studies/
15. (prospective or follow-up or cohort study or longitudinal study).ti,ab.
16. 14 or 15
17. 13 and 16
18. (exogenous or replacement or therapy or hormone treatment).ti.
19. Hormone Replacement Therapy/
20. 18 or 19
21. 17 not 20
22. limit 21 to humans
23. limit 22 to english language
24. limit 23 to (adaptive clinical trial or address or autobiography or bibliography or biography or case reports or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial, veterinary or clinical trials, veterinary as topic or clinical trial protocol or clinical trial or comment or controlled clinical trial or dictionary or editorial or lecture or legislation or meta analysis or practice guideline or pragmatic clinical trial or published erratum or randomized controlled trial or retracted publication or "retraction of publication" or "review" or "scientific integrity review" or "systematic review")
25. Retrospective Studies/ or Case-Control Studies/ or (retrospective analysis or case-control).ti.
26. 24 or 25
27. 23 not 26

Notes:

Terms with a trailing “/” are MeSH terms and those with a trailing “*” are truncated search strings. This search strategy has been submitted for registration on PROSPERO [Systematic Review Protocol ID 139668, submitted on 23 July 2019 and is presently being assessed]. Beforehand, a search of PROSPERO was conducted for another suitable strategy but none

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3 were found. However, the above strategy is based upon one that has been used for a similar
4 study.¹
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6 **References cited**

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**PRISMA-IPD Checklist of items to include when reporting a systematic review and meta-analysis of individual participant data (IPD):
the Androgens In Men Study (AIMS).**

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Title			
Title	1	Identify the report as a systematic review and meta-analysis of individual participant data.	1
Abstract			
Structured summary	2	Provide a structured summary including as applicable:	4-5
		Background: state research question and main objectives, with information on participants, interventions, comparators and outcomes.	
		Methods: report eligibility criteria; data sources including dates of last bibliographic search or elicitation, noting that IPD were sought; methods of assessing risk of bias.	
		Results: provide number and type of studies and participants identified and number (%) obtained; summary effect estimates for main outcomes (benefits and harms) with confidence intervals and measures of statistical heterogeneity. Describe the direction and size of summary effects in terms meaningful to those who would put findings into practice.	
		Discussion: state main strengths and limitations of the evidence, general interpretation of the results and any important implications.	
		Other: report primary funding source, registration number and registry name for the systematic review and IPD meta-analysis.	
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6-7
Objectives	4	Provide an explicit statement of the questions being addressed with reference, as applicable, to participants, interventions, comparisons, outcomes and study design (PICOS). Include any hypotheses that relate to particular types of participant-level subgroups.	8
Methods			
Protocol and registration	5	Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable.	5,9
Eligibility criteria	6	Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics (e.g. years when conducted, required minimum follow-up). Note whether these were applied at the study or individual level i.e. whether eligible participants were included (and ineligible participants excluded) from a study that included a wider population than specified by the review inclusion criteria. The rationale for criteria should be stated.	8-9

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Title			
Identifying studies - information sources	7	Describe all methods of identifying published and unpublished studies including, as applicable: which bibliographic databases were searched with dates of coverage; details of any hand searching including of conference proceedings; use of study registers and agency or company databases; contact with the original research team and experts in the field; open adverts and surveys. Give the date of last search or elicitation.	9
Identifying studies - search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	9, Suppl. Data
Study selection processes	9	State the process for determining which studies were eligible for inclusion.	9
Data collection processes	10	Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators. If IPD were not sought from any eligible study, the reason for this should be stated (for each such study). If applicable, describe how any studies for which IPD were not available were dealt with. This should include whether, how and what aggregate data were sought or extracted from study reports and publications (such as extracting data independently in duplicate) and any processes for obtaining and confirming these data with investigators.	10-11
Data items	11	Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought, including baseline and follow-up information. If applicable, describe methods of standardising or translating variables within the IPD datasets to ensure common scales or measurements across studies.	10-11
IPD integrity	A1	Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done.	10-11
Risk of bias assessment in individual studies.	12	Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. If applicable, describe how findings of IPD checking were used to inform the assessment. Report if and how risk of bias assessment was used in any data synthesis.	10-11
Specification of outcomes and effect measures	13	State all treatment comparisons of interests. State all outcomes addressed and define them in detail. State whether they were pre-specified for the review and, if applicable, whether they were primary/main or secondary/additional outcomes. Give the principal measures of effect (such as risk ratio, hazard ratio, difference in means) used for each outcome.	12-16
Synthesis methods	14	Describe the meta-analysis methods used to synthesise IPD. Specify any statistical methods and models used. Issues should include (but are not restricted to): <ul style="list-style-type: none"> • Use of a one-stage or two-stage approach. • How effect estimates were generated separately within each study and combined across studies (where applicable). 	13-16

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Title			
		<ul style="list-style-type: none"> • Specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for. • Use of fixed or random effects models and any other model assumptions, such as proportional hazards. • How (summary) survival curves were generated (where applicable). • Methods for quantifying statistical heterogeneity (such as I^2 and τ^2). • How studies providing IPD and not providing IPD were analysed together (where applicable). • How missing data within the IPD were dealt with (where applicable). 	
Exploration of variation in effects	A2	If applicable, describe any methods used to explore variation in effects by study or participant level characteristics (such as estimation of interactions between effect and covariates). State all participant-level characteristics that were analysed as potential effect modifiers, and whether these were pre-specified.	13-16
Risk of bias across studies	15	Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables.	10, 16
Additional analyses	16	Describe methods of any additional analyses, including sensitivity analyses. State which of these were pre-specified.	8, 16
Results			
Study selection and IPD obtained	17	Give numbers of studies screened, assessed for eligibility, and included in the systematic review with reasons for exclusions at each stage. Indicate the number of studies and participants for which IPD were sought and for which IPD were obtained. For those studies where IPD were not available, give the numbers of studies and participants for which aggregate data were available. Report reasons for non-availability of IPD. Include a flow diagram.	TBA
Study characteristics	18	For each study, present information on key study and participant characteristics (such as description of interventions, numbers of participants, demographic data, unavailability of outcomes, funding source, and if applicable duration of follow-up). Provide (main) citations for each study. Where applicable, also report similar study characteristics for any studies not providing IPD.	TBA
IPD integrity	A3	Report any important issues identified in checking IPD or state that there were none.	TBA
Risk of bias within studies	19	Present data on risk of bias assessments. If applicable, describe whether data checking led to the up-weighting or down-weighting of these assessments. Consider how any potential bias impacts on the robustness of meta-analysis conclusions.	TBA
Results of individual studies	20	For each comparison and for each main outcome (benefit or harm), for each individual study report the number of eligible participants for which data were obtained and show simple summary data for each intervention group (including, where applicable, the number of events), effect estimates and confidence intervals. These may be tabulated or included on a forest	TBA

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Title			
		plot.	
Results of syntheses	21	Present summary effects for each meta-analysis undertaken, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified, and report the numbers of studies and participants and, where applicable, the number of events on which it is based.	TBA
		When exploring variation in effects due to patient or study characteristics, present summary interaction estimates for each characteristic examined, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified. State whether any interaction is consistent across trials.	
		Provide a description of the direction and size of effect in terms meaningful to those who would put findings into practice.	
Risk of bias across studies	22	Present results of any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to the availability and representativeness of available studies, outcomes or other variables.	TBA
Additional analyses	23	Give results of any additional analyses (e.g. sensitivity analyses). If applicable, this should also include any analyses that incorporate aggregate data for studies that do not have IPD. If applicable, summarise the main meta-analysis results following the inclusion or exclusion of studies for which IPD were not available.	TBA
Discussion			
Summary of evidence	24	Summarise the main findings, including the strength of evidence for each main outcome.	TBA
Strengths and limitations	25	Discuss any important strengths and limitations of the evidence including the benefits of access to IPD and any limitations arising from IPD that were not available.	TBA
Conclusions	26	Provide a general interpretation of the findings in the context of other evidence.	TBA
Implications	A4	Consider relevance to key groups (such as policy makers, service providers and service users). Consider implications for future research.	TBA
Funding			
Funding	27	Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support.	20-21

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2 **A1 – A3 denote new items that are additional to standard PRISMA items. A4 has been created as a result of re-arranging content of the standard PRISMA**
3 **statement to suit the way that systematic review IPD meta-analyses are reported.**
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BMJ Open

Androgens In Men Study (AIMS): protocol for meta-analyses of individual participant data investigating associations of androgens with health outcomes in men.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-034777.R1
Article Type:	Protocol
Date Submitted by the Author:	28-Nov-2019
Complete List of Authors:	<p>Yeap, Bu; University of Western Australia, Medical School; Fiona Stanley Hospital, Department of Endocrinology and Diabetes Marriott, Ross; University of Western Australia, School of Population and Global Health Adams, Robert; Flinders University, Adelaide Institute for Sleep Health Antonio, Leen; KU Leuven, Clinical and Experimental Endocrinology Ballantyne, Christie; Baylor College of Medicine, Internal Medicine Bhasin, Shalender; Harvard Medical School Cawthon, PM; California Pacific Medical Center Research Institute, San Francisco Coordinating Center Couper, David; University of North Carolina at Chapel Hill, Gillings School of Global Public Health Dobs, Adrian; Johns Hopkins University, School of Medicine, Division of Endocrinology, Diabetes and Metabolism Flicker, Leon; University of Western Australia, WA Centre for Health & Ageing Karlsson, Magnus; Lund University, Department of Clinical Sciences and Orthopedic Surgery Martin, Sean A.; The University of Adelaide, Freemasons Foundation Centre for Men's Health Matsumoto, AM; VA Puget Sound Health Care System, Geriatric Research, Education and Clinical Center; University of Washington System, Medicine Mellström, Dan ; University of Gothenburg, Centre for Bone and Arthritis Research at the Sahlgrenska Academy, Institute of Medicine Norman, Paul; University of Western Australia, Medical School Ohlsson , C; University of Gothenburg, Centre for Bone and Arthritis Research at the Sahlgrenska Academy, Institute of Medicine Orwoll, Eric; Oregon Health & Science University O'Neill, Terence; The University of Manchester & NIHR Manchester Biomedical Research Centre, Centre for Epidemiology Versus Arthritis, Faculty of Biology, Medicine and Health; Manchester Academic Health Science Centre, Manchester University NHS Foundation Trust Shores, Molly; VA Puget Sound Health Care System; University of Washington, School of Medicine, Department of Psychiatry and Behavioral Sciences Travison, Thomas; Beth Israel Deaconess Medical Center, Institute for Aging Research, Hebrew SeniorLife; Harvard Medical School Vanderschueren, Dirk; Katholieke Universiteit Leuven, Department of</p>

	Chronic Diseases, Metabolism and Ageing (CHROMETA), Laboratory of Clinical and Experimental Endocrinology Wittert, Gary; The University of Adelaide, Freemasons Centre for Men's Health Wu, Frederick; The University of Manchester, Division of Diabetes, Endocrinology and Gastroenterology Murray, Kevin; University of Western Australia, School of Population and Global Health
Primary Subject Heading :	Diabetes and endocrinology
Secondary Subject Heading :	Epidemiology
Keywords :	Sex steroids & HRT < DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY, General endocrinology < DIABETES & ENDOCRINOLOGY

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3 1 Androgens In Men Study (AIMS): protocol for meta-analyses of individual participant data
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5 2 investigating associations of androgens with health outcomes in men.
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9
10 4 Corresponding author

11
12 5 Dr Bu B. Yeap MBBS, FRACP, PhD, Harry Perkins Institute of Medical Research, 11 Robin
13
14 6 Warren Drive, Murdoch 6150, Western Australia, Australia.

15
16
17 7 Email: bu.yeap@uwa.edu.au; Telephone: +61 8 6151 1149
18
19 8

20
21 9 Authors:

22
23
24 10 Bu B. Yeap, Medical School, The University of Western Australia, Perth 6009, Australia.

25
26 11 Ross J. Marriott, School of Population and Global Health, The University of Western
27
28 12 Australia, Perth 6009, Australia.

29
30 13 Robert J. Adams, Adelaide Institute for Sleep Health, Flinders University, Bedford Park
31
32 14 5042, Australia.

33
34 15 Leen Antonio, Clinical and Experimental Endocrinology, KU Leuven, Leuven, Belgium.

35
36 16 Christie M. Ballantyne, Internal Medicine, Baylor College of Medicine, Houston, Texas,
37
38 17 USA.

39
40 18 Shalender Bhasin, Harvard Medical School, Boston, Massachusetts, USA.

41
42 19 Peggy M. Cawthon, San Francisco Coordinating Center, California Pacific Medical Center
43
44 20 Research Institute, San Francisco, California, USA.

45
46 21 David J. Couper, Gillings School of Global Public Health, University of North Carolina at
47
48 22 Chapel Hill, Chapel Hill, North Carolina, USA.

49
50 23 Adrian S. Dobs, School of Medicine, Division of Endocrinology, Diabetes and Metabolism,
51
52 24 Johns Hopkins University, Baltimore, Maryland, USA.
53
54
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2
3 25 Leon Flicker, WA Centre for Health & Ageing, The University of Western Australia, Perth
4
5 26 6009, Australia.
6
7 27 Magnus Karlsson, Department of Clinical Sciences and Orthopedic Surgery, Lund
8
9 28 University, Lund, Sweden.
10
11 29 Sean A. Martin, Freemasons Foundation Centre for Men's Health, The University of
12
13 30 Adelaide, Adelaide 5000, Australia.
14
15 31 Alvin M. Matsumoto, Geriatric Research, Education and Clinical Center, VA Puget Sound
16
17 32 Health Care System, Seattle, Washington, USA.
18
19 33 Dan Mellström, Centre for Bone and Arthritis Research at the Sahlgrenska Academy,
20
21 34 Institute of Medicine, University of Gothenburg, Goteburg, Sweden.
22
23 35 Paul E. Norman, Medical School, The University of Western Australia, Fremantle 6160,
24
25 36 Australia.
26
27 37 Claes Ohlsson, Centre for Bone and Arthritis Research at the Sahlgrenska Academy, Institute
28
29 38 of Medicine, University of Gothenburg, Goteburg, Sweden.
30
31 39 Eric S. Orwoll, Oregon Health & Science University, Portland, Oregon, USA.
32
33 40 Terence W. O'Neill, Centre for Epidemiology Versus Arthritis, Faculty of Biology, Medicine
34
35 41 and Health, The University of Manchester & NIHR Biomedical Research Centre,
36
37 42 Manchester, United Kingdom.
38
39 43 Molly M. Shores, VA Puget Sound Health Care System, Seattle, Washington, United States.
40
41 44 Thomas G. Travison, Institute for Aging Research, Hebrew SeniorLife, Beth Israel
42
43 45 Deaconess Medical Center, Boston, Massachusetts, USA.
44
45 46 Dirk Vanderschueren, Department of Chronic Diseases, Metabolism and Ageing
46
47 47 (CHROMETA), Laboratory of Clinical and Experimental Endocrinology, Katholieke
48
49 48 Universiteit Leuven, Leuven, Flanders, Belgium.
50
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1
2
3 49 Gary A. Wittert, Freemasons Foundation Centre for Men's Health, The University of
4
5 50 Adelaide, Adelaide 5000, Australia.
6
7 51 Frederick C. W. Wu., Division of Diabetes, Endocrinology and Gastroenterology, The
8
9 52 University of Manchester, Manchester, United Kingdom.
10
11
12 53 Kevin Murray, School of Population and Global Health, The University of Western Australia,
13
14 54 Perth 6009, Australia.
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62 **ABSTRACT**

63 **Introduction**

64 This study aims to clarify the role(s) of endogenous sex hormones to influence health
65 outcomes in men, specifically to define the associations of plasma testosterone with incidence
66 of cardiovascular events, cancer, dementia and mortality risk, and to identify factors
67 predicting testosterone concentrations. Data will be accrued from at least three Australian,
68 two European, and four North American population-based cohorts involving approximately
69 20,000 men.

70 **Methods and analysis**

71 Eligible studies include prospective cohort studies with baseline testosterone concentrations
72 measured using mass spectrometry and five years of follow-up data on incident
73 cardiovascular events, mortality, cancer diagnoses or deaths, new onset dementia, or decline
74 in cognitive function recorded. Data for men, who were not taking androgens or drugs
75 suppressing testosterone production, metabolism, or action; and had no prior orchidectomy,
76 are eligible. No date range was set for searches. Aggregate level data will be sought where
77 individual participant data (IPD) is not available. One-stage IPD random-effects meta-
78 analyses will be performed, using linear mixed models, generalised linear mixed models and
79 either stratified or frailty-augmented Cox regression models. Heterogeneity in estimates from
80 different studies will be quantified and bias investigated using funnel plots. Effect size
81 estimates will be presented in forest plots and non-negligible heterogeneity and bias
82 investigated using subgroup or meta-regression analyses.

83 **Ethics and dissemination**

84 Ethics approvals obtained for each of the participating cohorts state that participants have
85 consented to have their data collected and used for research purposes. There are four planned

1
2
3 86 research articles, with each involving a separate set of IPD meta-analyses (articles will
4
5 87 investigate different, distinct outcomes).

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8 88 **Registration** PROSPERO Registration No. CRD42019139668.
9

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11 12 90 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

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14
15 91 • The IPD meta-analyses are likely to have higher statistical power than and provide greater
16
17 92 scope to control for important confounders and risk factors than previous meta-analyses
18
19 93 on this topic.
20
21 94 • Investigators from nine large prospective cohort studies (each with N > 1,000
22
23 95 participants) have agreed to collaborate., with additional studies to be identified from
24
25 96 systematic review.
26
27 97 • Harmonization will be required for some variables (e.g., physical activity, alcohol
28
29 98 consumption) that are recorded differently among the component studies, and aggregate-
30
31 99 level data will be sought where IPD-level data are not available.
32
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34
35 100 • As this is an observational study, it will not fully eliminate the possibility of confounding
36
37 101 influences of unadjusted effects.
38
39
40 102 • However, unlike a randomised controlled trial, this study will provide a more
41
42 103 comprehensive characterisation of temporal relationships between baseline androgen
43
44 104 concentrations and health outcomes in community-dwelling adult males.
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106 INTRODUCTION

107 As men grow older, testosterone production and circulating concentrations of testosterone
108 decline while comorbidities accumulate.[1-4] Older men, even those in very good health,
109 have lower circulating testosterone concentrations compared with healthy young men.[5, 6]
110 Although results have been inconsistent, an increasing number of studies have reported
111 associations of low endogenous testosterone concentration with poorer health outcomes,
112 especially in older men. For instance, studies that have used liquid chromatography tandem
113 mass spectrometry, widely regarded as the reference method for the measurement of total
114 testosterone concentrations,[7] have reported associations of lower endogenous testosterone
115 concentrations with: (i) cardiovascular disease and all-cause mortality in some cases[8-15]
116 but not others[8, 16-20]; (ii) some cancers but not others[21, 22]; and (iii) dementia[23, 24]
117 but not laboratory measures of cognitive function.[25] Therefore it remains unclear whether
118 testosterone is a biomarker of ill-health or a causal factor for diseases of ageing.

119
120 Currently, testosterone treatment is recommended for men who have symptoms and signs of
121 androgen deficiency and low testosterone concentrations, due to disease of the hypothalamus,
122 pituitary or testes (organic or pathological hypogonadism).[26-29] Randomised controlled
123 trials of testosterone treatment in men aged 65 and older with low-normal testosterone
124 concentrations without organic hypogonadism have shown modest benefits on sexual
125 function, anaemia, self-reported physical function and mobility, and volumetric bone density,
126 but not on some objective measures of cognition over 12 to 36 months.[30-34] The effect of
127 testosterone on major adverse cardiovascular events remains unclear.[35, 36] However, the
128 selection criteria of these trials was such that the screening to enrolment ratio was 65:1, a
129 highly selected population of older men.[32, 33, 36] Importantly, the trials were neither large
130 enough nor long enough to determine the effects of testosterone on major adverse

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3 131 cardiovascular events, development of dementia, bone fractures, and mortality.[36]
4
5 132 Therefore, a meta-analysis of data from prospective cohort studies, with extended follow-up
6
7 133 periods, provides opportunities for better understanding of the temporal profiles of the
8
9
10 134 postulated associations between endogenous testosterone concentration and incident health
11
12 135 outcomes. Meta-analyses of Individual Participant Data (IPD) are generally preferable to
13
14 136 meta-analyses of aggregate data in that they typically have higher statistical power and
15
16
17 137 provide scope to control for important confounders and risk factors.[37, 38] Furthermore,
18
19 138 one-stage IPD meta-analyses are preferable to two-stage approaches because the former uses
20
21 139 an exact likelihood to directly model the distribution of IPD, offers the convenience of using
22
23 140 a standard set of diagnostic tools to assess model fit, and can arguably provide greater
24
25
26 141 flexibility, in terms of options for statistical modelling.[39, 40]
27
28 142
29
30 143 The Androgens In Men Study (AIMS), an international collaboration of prospective cohort
31
32 144 studies, will examine the associations of sex hormones (comprising testosterone and
33
34 145 dihydrotestosterone as the major androgens, and estradiol as the major estrogen, in the
35
36 146 circulation) with health outcomes that are major sources of morbidity and mortality in
37
38 147 middle-aged and older men. The group will perform a series of IPD meta-analyses to clarify
39
40 148 the influence of sex hormone exposures on major health outcomes, including heart attack,
41
42 149 stroke and cardiovascular deaths, cancer, new-onset dementia, and all-cause mortality, as
43
44 150 well as provide information on social, demographic and behavioural factors that are
45
46 151 associated with endogenous testosterone concentrations. This work will characterise robustly
47
48 152 the associations of several sex hormones with health outcomes in men in general over and
49
50 153 above the study-specific estimates, and thus clarify the role of androgens as biomarkers for,
51
52 154 or causal contributors to, men's health. The work outlined in this document will be conducted
53
54 155 from 1 February 2019 to 30 November 2020.
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157 Objectives

158 The Androgens In Men Study (AIMS) will establish an international collaboration of existing
159 cohort studies to clarify the relation of endogenous sex hormones with major health outcomes
160 in men. PEO (Population, Exposure, Outcomes) characteristics include: adult men in the
161 general community; an exposure of endogenous circulating sex hormone concentration,
162 primarily testosterone, as the principal male sex hormone or androgen; and a prospective
163 cohort study type, with incident health outcomes including incidence of cardiovascular
164 disease events, mortality, cancers, and dementia. The specific objectives of the AIMS study
165 are: to investigate associations between variables representing social, demographic, and
166 behavioural factors with the measured concentration of testosterone in the blood of men
167 (Analysis 1); to examine the associations between testosterone concentrations and subsequent
168 incidence of cardiovascular events, cardiovascular deaths, and all-cause mortality in men
169 (Analysis 2); to examine the associations between testosterone concentrations and subsequent
170 mortality from (and, if available, diagnoses of) common cancers in men (Analysis 3); to
171 examine the associations between testosterone concentrations and cognitive impairment and
172 incident dementia in men (Analysis 4). Analysis 2 will evaluate myocardial infarction, stroke
173 and heart failure, deaths due to cardiovascular disease, and the composite endpoint of major
174 adverse cardiovascular events (MACE) comprising non-fatal myocardial infarction, non-fatal
175 stroke, and deaths due to cardiovascular disease. Analysis 3 will evaluate outcomes of deaths
176 due to and diagnoses of colorectal cancer, lung cancer and prostate cancer.

177

178 **METHODS AND ANALYSIS**

179 IPD meta-analyses will be conducted to understand the associations between testosterone and
180 a range of associated major health outcomes in men. IPD meta-analyses have been selected
181 as the most suitable approach because: (i) the required aggregate data (AD) are not available
182 from each of the cohorts in published literature; (ii) IPD meta-analyses typically have higher
183 statistical power than AD meta-analyses and provide scope for controlling for important
184 confounders and risk factors.[37, 38] Where possible, methods will adhere to the guidelines
185 for Preferred Reporting Items for Systematic Reviews and Meta-Analyses of IPD data
186 (PRISMA-IPD; completed checklist is provided in Supplementary Material) and the Meta-
187 analysis Of Observational Studies in Epidemiology (MOOSE).[41-43]

188

189 **Studies selected for inclusion in IPD meta-analyses**

190 Studies will be identified from a systematic review using online search tools for mainstream
191 published (MEDLINE, EMBASE) and grey literature (OpenGrey, Mednar) studies. Eligible
192 studies include prospective cohort studies with plasma or serum testosterone concentrations
193 measured using mass spectrometry with at least five years of follow-up data, with incident
194 cardiovascular, cancer, mortality, dementia, or cognitive events recorded (see Supplementary
195 Table S1 for an example of search criteria to be used). The search strategy selects for articles
196 based on words or Medical Subject Headings (MeSH) terms matching the relevant exposure
197 (example steps 1-3), outcomes (example steps 4-10), and study type (example steps 14-15),
198 then, depending on the search tool, filters down to more relevant studies, with exclusions of
199 clinical trials and of studies on non-humans (example steps 18-27), with no date range
200 restrictions. Ahead of the systematic review, nine eligible studies (cohorts) had expressed
201 interest to collaborate: three from Australia (Busselton Health Study BHS, Health In Men
202 Study HIMS, Men Androgen Inflammation Lifestyle Environment and Stress study

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3 203 MAILES); two from Europe (European Male Ageing Study EMAS, Osteoporotic Fractures in
4
5 204 Men Study MrOS - Sweden); and four from the USA (Atherosclerosis Risk in Communities
6
7 205 study ARIC, Cardiovascular Health Study CHS, The Framingham Heart Study FHS,
8
9 206 Osteoporotic Fractures in Men Study MrOS - USA). Investigators from eight of these studies
10
11 207 have confirmed availability of suitable IPD-level data, provisional on approvals from their
12
13 208 respective Publication and Steering Committees. If it is not possible to obtain IPD-level data
14
15 209 from selected studies, we will request suitable AD-level data.
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211 **Data provision, merging, harmonisation, and storage**

23
24 212 The project manager will liaise directly with the nominated contact person for each cohort
25
26 213 study to identify, specifically, which variables and set of observations will be suitable to
27
28 214 request. A data request will then be submitted to the data custodian for each study. Requested
29
30 215 variables will be labelled as either “highly desirable” or “only if available”, in order to
31
32 216 prioritise efforts in obtaining the key variables for analyses and to acknowledge the differing
33
34 217 availability of variables among studies. A list of variable names, definitions, and attributes,
35
36 218 including numbers of rows and columns in each data file(s) will also be requested to be
37
38 219 provided separately. Methods for ascertaining outcome and comorbidity status will be
39
40 220 requested, which can be used to indicate the relative quality of diagnostic information (e.g.
41
42 221 ICD-coded diagnoses from hospital inpatient admissions versus self-report information). File
43
44 222 transfer will be achieved via encrypted file transfer (or other sufficiently secure method).
45
46
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223

50
51 224 Once each dataset has been received by the project manager, the original file(s) will be saved
52
53 225 and date-stamped in a secure central repository. All subsequent manipulations will be
54
55 226 completed using copies of the original file, with syntax saved as script files. Variable
56
57 227 definitions will be checked, variables inspected for missing values, and variable properties
58
59
60

1
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3 228 and value ranges assessed to identify possible outliers. A table of summary statistics will be
4
5 229 calculated and, where possible, analyses run and compared with published values to check for
6
7 230 data consistency. The nature of any discrepancies identified from these checks will need to be
8
9
10 231 understood, and possibly resolved, prior to proceeding with the meta-analyses.[42, 44, 45]
11
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13 232
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16 233 Depending on the extent of missing-ness, missing data will be suitably imputed.[45, 46] For
17
18 234 each analysis, we will conduct multiple imputations using a method that approximates as
19
20 235 close as possible to the substantive model.[47] The method will likely vary depending on the
21
22 236 analysis[48] and therefore we will consider adapting either a Fully Conditional Specification
23
24 237 (e.g., [49]) or Joint Modelling framework (e.g., [50]) to each case, as is appropriate. The
25
26 238 quality of imputations will be quantified by using re-imputed values to calculate the posterior
27
28 239 predictive p-values of relevant quantities.[51] Results from each of the multiply-imputed
29
30 240 datasets will be suitably pooled to obtain final estimates, standard errors, and 95% confidence
31
32 241 intervals.[52]
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40 243 Prior to the merging of datasets, a variable to identify each source study will be appended as
41
42 244 the new first column. Variable formats will be checked and corrected for consistency and
43
44 245 anonymised participant identifier codes for uniqueness across all studies. Harmonization will
45
46 246 be required for some variables (e.g., physical activity, alcohol consumption) that are recorded
47
48 247 differently by the different component studies. Where possible, AD datasets will be used to
49
50 248 reconstruct IPD-level data (that is, partially-reconstructed IPD) prior to merging.[53-55]
51
52
53 249 Should this not be possible, the IPD-level data will be aggregated and summary estimates
54
55 250 made with and without AD-level data as sensitivity analyses. It is also possible that some
56
57 251 studies might have outcomes available for some analyses, but not others; in these cases, we
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3 252 will preferentially use IPD-level data when available but also seek to use AD-level data from
4
5 253 those other studies when available. There is no requirement to use IPD-level data from the
6
7
8 254 same studies across all analyses.
9

10 255
11
12 256 All IPD-level data will be accessible to only the approved staff from a secure on-site facility,
13
14 257 from rooms that are kept locked when unattended, and with remote access not permitted.
15
16 258 IPD-level data are not to be printed in hard copy and will only be presented at aggregate
17
18 259 level. Data analysed for this study will be retained for five years after the last of all proposed
19
20 260 analyses are published and will then be destroyed. A post-analysis retention period is required
21
22 261 to enable publication and possible scrutiny of findings. Disposal will be carried out according
23
24
25 262 to best practice.
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29 263

30 31 32 264 **Data items** 33

34
35 265 The full list of generic variables to include in meta-analyses are presented in Table 1.
36
37 266 Analysis 1 will model relationships of total testosterone concentrations, as measured in serum
38
39 267 or plasma samples (dependent variable), with key demographic variables and risk factors for
40
41 268 disease (predictor variables). Time-to-event variables obtained from follow-up data will be
42
43 269 analysed in Analysis 2 and 3 (outcomes), and their associations with testosterone
44
45 270 concentrations (focal predictor) and other potential confounders and risk factors (predictor
46
47 271 variables). Records of dementia diagnoses (physician or otherwise categorised) and relative
48
49 272 cognitive function (for example, from test scores) will be analysed in Analysis 4, and their
50
51 273 associations with testosterone concentrations and other potential confounders and risk factors.
52
53
54 274 Analyses of relationships with other sex hormones instead of testosterone, including
55
56 275 dihydrotestosterone, estradiol, luteinising hormone (LH), and Sex Hormone Binding Globulin
57
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3 276 (SHBG), will be conducted where sufficient data is available. For exploratory analyses, free
4
5 277 testosterone, the amount in the circulation which is not protein-bound, will be calculated from
6
7 278 measured total testosterone and SHBG.[56] Covariates were selected to include those used in
8
9
10 279 previous studies, as well as those that are typically recorded. The full list of proposed
11
12 280 variables to include in the meta-analyses are presented in Table 1.
13
14
15 281

17 282 **Statistical analysis**

18
19
20 283 Since the datasets to be analysed are sampled from different populations, a random-effects
21
22 284 meta-analysis is appropriate, as it acknowledges that effects will vary among studies due to
23
24 285 differences in local factors.[57] One-stage IPD meta-analyses will be performed. Each IPD
25
26 286 meta-analysis will involve fitting a model with study estimated as either a fixed or random
27
28 287 term, to account for related observations within studies, and testosterone modelled as random
29
30
31 288 slopes (when modelled as a continuous predictor) or intercepts (when modelled as a
32
33 289 categorical predictor), to harmonised, merged data from all cohorts. The underlying statistical
34
35
36 290 model and estimates of effect size will be specific to each of the proposed analyses and are
37
38 291 outlined as follows.
39
40
41 292

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43
44 293 *Analysis 1: Factors associated with testosterone concentrations in men and characterisation*
45
46 294 *of reference ranges.*

47
48
49 295 Linear Mixed Models (LMMs) or Generalised Linear Mixed Models (GLMMs) will be used
50
51 296 to model the relation between the predictors (independent variables) and each hormonal
52
53 297 variable (testosterone, dihydrotestosterone, estradiol, LH, SHBG) as five separate IPD meta-
54
55 298 analyses. Suspected non-linear relationships, at the scale of the linear predictor, will be
56
57
58 299 investigated and modelled appropriately (e.g., splines with pre-set knot locations and linear
59
60

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3 300 boundary constraints). Measures of effect size may include (but are not limited to): η^2 , [58,
4
5 301 59] Pearson's r , standardised mean difference to the reference level (categorical predictors),
6
7 302 standardised difference for an increase in one standard deviation (continuous predictors). In
8
9 303 the case of non-linear relations, we will graphically describe the relationship with
10
11 304 comparisons made with appropriate reference points. Reference ranges will be derived based
12
13 305 on the distributions of testosterone in healthy men.
14
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18 306

19
20 307 *Analysis 2: Associations between testosterone concentrations and subsequent incidence of*
21
22 308 *cardiovascular events, cardiovascular deaths, and all-cause mortality.*
23
24

25 309 Cox proportional hazards models will be used to assess the effect of testosterone level on the
26
27 310 incident risk of each outcome, with separate IPD meta-analyses conducted for each outcome
28
29 311 (myocardial infarction, stroke, heart failure, deaths due to cardiovascular disease, and
30
31 312 MACE) and each hormonal variable (testosterone, dihydrotestosterone, estradiol, LH,
32
33 313 SHBG). Component study will be modelled either as a stratified variable [39] or as a random
34
35 314 term, and testosterone as a random term, using frailty models, which are a class of survival
36
37 315 models that incorporate random effects. [60-62] Participants with prevalent cardiovascular
38
39 316 disease at baseline will be excluded. The length of follow-up will also be standardised among
40
41 317 studies in order to maximise data from all datasets, whilst minimising the prospect for
42
43 318 variable lengths-to-follow-up among studies introducing additional heterogeneity into
44
45 319 results. [46]
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53
54 321 Multivariable versions of each of these models will also be fitted, with additional predictors
55
56 322 for potential confounders and risk factors included (Table 1). Non-linear associations for
57
58 323 continuous variables will be modelled using natural splines with pre-specified knots and
59
60

1
2
3 324 linear boundary constraints. The (standardised) measure of effect size used will be the hazard
4
5 325 ratio. Subgroup analyses will be conducted separately for each of three specific types of
6
7 326 cardiovascular disease (outcomes): myocardial infarction, stroke and heart failure.
8
9

10
11 327

12
13 328 *Analysis 3: Association between testosterone level and subsequent incidence of cancer.*

14
15 329 Cox proportional hazards models will be used to assess the effect of testosterone

16
17 330 concentrations on the incident risk of cancer deaths and, if available, of cancer diagnoses.

18
19 331 IPD meta-analyses separately conducted for each of these outcomes and each hormonal

20
21 332 variable as focal predictor (testosterone, dihydrotestosterone, estradiol, LH, SHBG).

22
23 333 Component study will be modelled either as a stratified variable[39] or as a random term, and

24
25 334 testosterone as a random term, using frailty models.[60-62] Participants with prevalent cancer

26
27 335 diagnosis at baseline will be excluded. The length of follow-up will be standardised among

28
29 336 studies in order to maximise data from all datasets, whilst minimising the prospect for

30
31 337 variable lengths-to-follow-up among studies introducing additional heterogeneity into

32
33 338 results.[46]
34
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41 340 Multivariable versions of each of these models will also be fitted, with additional predictors

42
43 341 for potential confounders and risk factors included (Table 1). Non-linear associations for

44
45 342 continuous variables will be modelled using natural splines with pre-specified knots and

46
47 343 linear boundary constraints. The (standardised) measure of effect size used will be the hazard

48
49 344 ratio. Subgroup analyses will be conducted separately for each of three common types of

50
51 345 cancers in men (outcomes): colorectal cancer, lung cancer, prostate cancer. For these

52
53 346 analyses, men with the relevant cancer type at baseline will be excluded from that specific

54
55 347 analysis. Thus men with prevalent colorectal cancer (but not other cancer types) will be
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3 348 excluded in the analysis of incident colorectal cancer; similarly for the analyses of incident
4
5 349 lung and prostate cancer, men with lung or prostate cancer at baseline will be excluded.
6
7

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9
10 351 *Analysis 4: Associations of testosterone levels with cognitive impairment and incident*
11
12
13 352 *dementia in men.*
14

15 353 LMMs and GLMMs will be used to model the association of testosterone concentrations with
16
17 354 cognitive impairment (cross-sectional analyses of baseline data). Cox proportional hazards
18
19 355 models will be used to assess the effect of testosterone concentrations on the incident risk of
20
21 356 dementia. Men with prevalent dementia will be excluded from this analysis. We will also ask
22
23 357 for follow-up cognition test scores, and if available, will run an analysis of changes in
24
25 358 cognition test scores from baseline as an outcome. Separate IPD meta-analyses will be
26
27 359 conducted for each hormonal variable as a focal predictor (testosterone, dihydrotestosterone,
28
29 360 estradiol, LH, SHBG). Component study will be modelled as a fixed or random intercept
30
31 361 term in LMMs and GLMMs and as a stratified factor or frailty model random term in Cox
32
33 362 regressions. Multivariable versions of each of these models will also be fitted, with additional
34
35 363 predictors for potential confounders and risk factors included (Table 1). Suspected non-linear
36
37 364 relationships, at the scale of the linear predictor, will be investigated and modelled using
38
39 365 splines with pre-specified knots and boundary constraints. Measures of effect size may
40
41 366 include: η^2 , Pearson's r , standardised mean difference to the reference level (categorical
42
43 367 predictors), standardised difference for an increase in one standard deviation (continuous
44
45 368 predictors), odds ratio for LMMs and GLMMs and hazard ratio for Cox regressions.
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53 370 Throughout all analyses, contour-enhanced funnel plots will be constructed to visually assess
54
55 371 patterns in estimates of effect sizes and precision among studies, to investigate heterogeneity
56
57
58 372 and possible meta-biases.[63-65] The relative amount of heterogeneity will be estimated
59
60

1
2
3 373 (e.g., using I^2) and forest plots presented. Subgroup or meta-regression analyses may be
4
5 374 conducted if pronounced heterogeneity is estimated.[57]
6
7
8 375

9
10 376 **Patient and public involvement**

11
12 377 This IPD meta-analysis will use existing secondary data. Patients and public were not
13
14 378 involved in the design, recruitment or conduct of this IPD meta-analysis. The results of this
15
16 379 study will be shared with the primary investigators of the shared studies and disseminated as
17
18 380 publications in open-access journals.
19
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21 381

22
23
24 382 **ETHICS AND DISSEMINATION**

25
26 383 Ethics approvals obtained for each of the participating cohorts state that participants have
27
28 384 consented to have their data collected and used for research purposes. Furthermore, there are
29
30 385 no expected harms or risks to participants, as data have already been collected within each
31
32 386 individual cohort, under existing ethics approvals. De-identified data will be collated and
33
34 387 analysed, with no new procedures planned for participants. The AIMS study has been
35
36 388 assessed as exempt from ethics review by the Human Research Ethics Office at the
37
38 389 University of Western Australia (file reference number RA/4/20/5014).
39
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41 390

42
43
44 391 **DISCUSSION**

45
46 392 Although several published meta-analyses have investigated associations of endogenous
47
48 393 testosterone with health outcomes in men,[66-77] none have conducted IPD meta-analyses of
49
50 394 health outcomes as planned for this study. A previous IPD meta-analysis focussed on the
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52 395 outcome of metabolic syndrome.[69] Results from this study will improve upon previously
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54 396 published estimates from individual studies, in terms of the generalisability of findings.
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56 397 Estimates from the IPD meta-analyses are also likely to be more reliable than those published
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3 398 from conventional meta-analyses because they typically have higher statistical power and
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5 399 provide scope for controlling for important confounders and risk factors.[37, 38] Uncertainty
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7 400 will undoubtedly remain due to the possibility of confounding influences of unadjusted
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9 401 effects. However, unlike a randomised controlled trial, this study avoids the need to subject
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11 402 individuals to interventions, and provides more comprehensive characterisation of temporal
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13 403 relationships between baseline testosterone concentrations and a range of key health
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15 404 outcomes.[78]
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21 406 Accordingly, it is hoped that the AIMS collaboration will ultimately complement the research
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23 407 efforts and outputs from multiple prospective cohort studies by drawing upon the collective
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25 408 body of evidence to clarify the role of endogenous sex hormone levels on major health
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27 409 outcomes in men. It is possible that this work might also elucidate new understanding, arising
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29 410 from improved scope for fitting more complex models due to increased statistical power, or
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31 411 from patterns detected in subgroup or meta-regression analyses. Clinically, research outputs
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33 412 will be used to identify the scope and optimal recruitment criteria for future trials of
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35 413 testosterone therapy. These data will also allow reference ranges for testosterone in men
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37 414 across ages and geographical locations to be refined, to inform recommendations for clinical
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39 415 practice more generally.
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14
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16
17 429 Charles Gairdner Hospital, Nedlands WA 6009, Australia (2) Health In Men Study (HIMS):
18
19 430 Western Australian Centre for Health and Ageing, University of Western Australia, Level 6
20
21 431 Medical Research Foundation Building, Royal Perth Hospital, Rear 50 Murray Street, Perth,
22
23 432 Western Australia 6000, Australia. (3) Men Androgen Inflammation Lifestyle Environment
24
25 433 and Stress (MAILES) study: Freemasons Foundation Centre for Men's Health, University of
26
27 434 Adelaide, 254 North Tce, Adelaide, Australia. (4) European Male Ageing Study (EMAS):
28
29 435 The University of Manchester, Stopford Building, Oxford Road, Manchester, M13 9PT, UK.
30
31 436 (5) Osteoporotic Fractures in Men (MrOS) Study Sweden: Department of Clinical Sciences
32
33 437 and Orthopedic Surgery, Lund University, Skåne University Hospital, Malmö, Sweden;
34
35 438 MrOS Study USA: California Pacific Medical Center Research Institute, San Francisco
36
37 439 Coordinating Center, 550 16th street, San Francisco, CA 94143. (6) Atherosclerosis Risk in
38
39 440 Communities study (ARIC): School of Public Health, U. of North Carolina, Suite 2013,
40
41 441 NCNB Plaza, 137 E. Franklin St, Chapel Hill, NC 27514. (7) Cardiovascular Health Study:
42
43 442 National Heart, Lung, and Blood Institute, Bethesda, MD. (8) The Framingham Heart Study,
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45 443 Boston University School of Medicine, 72 E. Concord Street, B-601, Boston, MA 02118.
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3 445 **Authors' contributions**
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10 499 **Patient consent**
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12 500 Each of the component studies have addressed participant/patient consent permissions; please
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14 501 refer to respective component studies for details.[79-86]
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19 503 **Ethics approval**
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731 TABLES

732 Table 1. Variables planned to be included in IPD meta-analysis modelling.¶¶

Type	Analysis 1	Analysis 2	Analysis 3	Analysis 4
Outcomes / DV	Androgen concentration§	Incident CVD*	Incident deaths (cancer*)	Incident dementia
		Incident deaths (CVD*)	Incident cancer* (diagnoses)	Baseline cognition
		Incident deaths (all-cause)		Change in cognition
Focal predictor	-	Androgen concentration§	Androgen concentration§	Androgen concentration§
Covariates / IV				
Demographic	age	age	age	age
	education level	education level	education level	education level
	ethnicity	ethnicity	ethnicity	ethnicity
	marital status	marital status	marital status	marital status
	site	site	site	site
Risk factors and comorbidities	alcohol consumption	alcohol consumption	alcohol consumption	alcohol consumption
	BMI, waist	BMI, waist	BMI, waist	BMI, waist
	physical activity	physical activity	physical activity	physical activity
	smoking status	smoking status	smoking status	smoking status
	BP, hypertension	BP, hypertension	BP, hypertension	BP, hypertension
	general health	general health atrial fibrillation	general health	general health
	prevalent CVD	prevalent CVD		
	prevalent cancer*		prevalent cancer*	
	prevalent dementia			prevalent dementia
	baseline cognition			
	COPD	COPD		
	diabetes	diabetes	diabetes	diabetes
	cholesterol, LDL, HDL	cholesterol, LDL, HDL		
	creatinine level	creatinine level		
	lipid lowering medications	lipid lowering medications		
	anxiety			anxiety
	depression			depression
	psychotropic drug use			psychotropic drug use

733 **Abbreviations:** BMI = body mass index; BP= blood pressure; CVD = Cardiovascular
734 Disease; DV = dependent variable; COPD = Chronic Obstructive Pulmonary Disease;
735 IV = independent variables.

736 ¶¶ = Black font: highly desirable; Green font: only if available.

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3 737 § = Androgens: total testosterone, dihydrotestosterone, estradiol, luteinising hormone, sex
4 738 hormone binding globulin.
5 739 * = Subgroup analyses are also planned. For CVD outcomes: Heart Failure, Myocardial
6 740 Infarction, Stroke. For cancer outcomes: colorectal cancer, lung cancer, prostate
7 741 cancer.
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Supplementary Table S1. Example search strategy for systematic review: AIMS study.

The following is the search strategy for MEDLINE. The search strategy for EMBASE, OpenGrey, and Mednar attempts to replicate this as closely as possible, and will be subsequently reported upon completion of the Systematic Review.

1. Testosterone/ or Androgens/
2. (testosterone or androgen* or sex hormone* or sex steroid*).ti.
3. (testosterone or androgen*).ab.
4. cardiovascular diseases/ or heart diseases/ or heart failure/ or vascular diseases/ or stroke/ or myocardial infarction/ or coronary disease/ or cerebrovascular disorders/
5. (cardiovascular or stroke or myocardial infarction or heart failure).ti.
6. neoplasms/ or colorectal neoplasms/ or lung neoplasms/ or prostatic neoplasms/
7. cancer.ti.
8. mortality/ or mortality.ti.
9. dementia/ or cognition/ or dementia.ti. or cognit*.ti.
10. Aging/psychology or Neuropsychological Tests/
11. 1 or 2 or 3
12. 4 or 5 or 6 or 7 or 8 or 9 or 10
13. 11 and 12
14. longitudinal studies/ or prospective studies/ or follow-up studies/ or cohort studies/
15. (prospective or follow-up or cohort study or longitudinal study).ti,ab.
16. 14 or 15
17. 13 and 16
18. (exogenous or replacement or therapy or hormone treatment).ti.
19. Hormone Replacement Therapy/
20. 18 or 19
21. 17 not 20
22. limit 21 to humans
23. limit 22 to english language
24. limit 23 to (adaptive clinical trial or address or autobiography or bibliography or biography or case reports or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial, veterinary or clinical trials, veterinary as topic or clinical trial protocol or clinical trial or comment or controlled clinical trial or dictionary or editorial or lecture or legislation or meta analysis or practice guideline or pragmatic clinical trial or published erratum or randomized controlled trial or retracted publication or "retraction of publication" or "review" or "scientific integrity review" or "systematic review")
25. Retrospective Studies/ or Case-Control Studies/ or (retrospective analysis or case-control).ti.
26. 24 or 25
27. 23 not 26

Notes:

Terms with a trailing "/" are MeSH terms and those with a trailing "*" are truncated search strings. This search strategy is included with the PROSPERO registration for the AIMS

1
2
3 project (Registration No. CRD42019139668). Beforehand, a search of PROSPERO was
4 conducted for another suitable strategy but none were found. However, the above strategy is
5 based upon one that has been used for a similar study.¹
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8 **References cited**

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**PRISMA-IPD Checklist of items to include when reporting a systematic review and meta-analysis of individual participant data (IPD):
the Androgens In Men Study (AIMS).**

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Title			
Title	1	Identify the report as a systematic review and meta-analysis of individual participant data.	1
Abstract			
Structured summary	2	Provide a structured summary including as applicable:	4-5
		Background: state research question and main objectives, with information on participants, interventions, comparators and outcomes.	
		Methods: report eligibility criteria; data sources including dates of last bibliographic search or elicitation, noting that IPD were sought; methods of assessing risk of bias.	
		Results: provide number and type of studies and participants identified and number (%) obtained; summary effect estimates for main outcomes (benefits and harms) with confidence intervals and measures of statistical heterogeneity. Describe the direction and size of summary effects in terms meaningful to those who would put findings into practice.	
		Discussion: state main strengths and limitations of the evidence, general interpretation of the results and any important implications.	
		Other: report primary funding source, registration number and registry name for the systematic review and IPD meta-analysis.	
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6-7
Objectives	4	Provide an explicit statement of the questions being addressed with reference, as applicable, to participants, interventions, comparisons, outcomes and study design (PICOS). Include any hypotheses that relate to particular types of participant-level subgroups.	8
Methods			
Protocol and registration	5	Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable.	5
Eligibility criteria	6	Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics (e.g. years when conducted, required minimum follow-up). Note whether these were applied at the study or individual level i.e. whether eligible participants were included (and ineligible participants excluded) from a study that included a wider population than specified by the review inclusion criteria. The rationale for criteria should be stated.	9

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Title			
Identifying studies - information sources	7	Describe all methods of identifying published and unpublished studies including, as applicable: which bibliographic databases were searched with dates of coverage; details of any hand searching including of conference proceedings; use of study registers and agency or company databases; contact with the original research team and experts in the field; open adverts and surveys. Give the date of last search or elicitation.	9
Identifying studies - search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	9, Suppl. Data
Study selection processes	9	State the process for determining which studies were eligible for inclusion.	9
Data collection processes	10	Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators. If IPD were not sought from any eligible study, the reason for this should be stated (for each such study).	10-12
		If applicable, describe how any studies for which IPD were not available were dealt with. This should include whether, how and what aggregate data were sought or extracted from study reports and publications (such as extracting data independently in duplicate) and any processes for obtaining and confirming these data with investigators.	
Data items	11	Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought, including baseline and follow-up information. If applicable, describe methods of standardising or translating variables within the IPD datasets to ensure common scales or measurements across studies.	12-13
IPD integrity	A1	Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done.	10-11
Risk of bias assessment in individual studies.	12	Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. If applicable, describe how findings of IPD checking were used to inform the assessment. Report if and how risk of bias assessment was used in any data synthesis.	10-11,16-17
Specification of outcomes and effect measures	13	State all treatment comparisons of interests. State all outcomes addressed and define them in detail. State whether they were pre-specified for the review and, if applicable, whether they were primary/main or secondary/additional outcomes. Give the principal measures of effect (such as risk ratio, hazard ratio, difference in means) used for each outcome.	13-16
Synthesis methods	14	Describe the meta-analysis methods used to synthesise IPD. Specify any statistical methods and models used. Issues should include (but are not restricted to): <ul style="list-style-type: none"> • Use of a one-stage or two-stage approach. • How effect estimates were generated separately within each study and combined across studies (where applicable). 	13-16

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Title			
		<ul style="list-style-type: none"> • Specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for. • Use of fixed or random effects models and any other model assumptions, such as proportional hazards. • How (summary) survival curves were generated (where applicable). • Methods for quantifying statistical heterogeneity (such as I^2 and τ^2). • How studies providing IPD and not providing IPD were analysed together (where applicable). • How missing data within the IPD were dealt with (where applicable). 	
Exploration of variation in effects	A2	If applicable, describe any methods used to explore variation in effects by study or participant level characteristics (such as estimation of interactions between effect and covariates). State all participant-level characteristics that were analysed as potential effect modifiers, and whether these were pre-specified.	13-16
Risk of bias across studies	15	Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables.	10, 16
Additional analyses	16	Describe methods of any additional analyses, including sensitivity analyses. State which of these were pre-specified.	8, 16-17
Results			
Study selection and IPD obtained	17	Give numbers of studies screened, assessed for eligibility, and included in the systematic review with reasons for exclusions at each stage. Indicate the number of studies and participants for which IPD were sought and for which IPD were obtained. For those studies where IPD were not available, give the numbers of studies and participants for which aggregate data were available. Report reasons for non-availability of IPD. Include a flow diagram.	TBA
Study characteristics	18	For each study, present information on key study and participant characteristics (such as description of interventions, numbers of participants, demographic data, unavailability of outcomes, funding source, and if applicable duration of follow-up). Provide (main) citations for each study. Where applicable, also report similar study characteristics for any studies not providing IPD.	TBA
IPD integrity	A3	Report any important issues identified in checking IPD or state that there were none.	TBA
Risk of bias within studies	19	Present data on risk of bias assessments. If applicable, describe whether data checking led to the up-weighting or down-weighting of these assessments. Consider how any potential bias impacts on the robustness of meta-analysis conclusions.	TBA
Results of individual studies	20	For each comparison and for each main outcome (benefit or harm), for each individual study report the number of eligible participants for which data were obtained and show simple summary data for each intervention group (including, where applicable, the number of events), effect estimates and confidence intervals. These may be tabulated or included on a forest	TBA

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Title			
		plot.	
Results of syntheses	21	Present summary effects for each meta-analysis undertaken, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified, and report the numbers of studies and participants and, where applicable, the number of events on which it is based.	TBA
		When exploring variation in effects due to patient or study characteristics, present summary interaction estimates for each characteristic examined, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified. State whether any interaction is consistent across trials.	
		Provide a description of the direction and size of effect in terms meaningful to those who would put findings into practice.	
Risk of bias across studies	22	Present results of any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to the availability and representativeness of available studies, outcomes or other variables.	TBA
Additional analyses	23	Give results of any additional analyses (e.g. sensitivity analyses). If applicable, this should also include any analyses that incorporate aggregate data for studies that do not have IPD. If applicable, summarise the main meta-analysis results following the inclusion or exclusion of studies for which IPD were not available.	TBA
Discussion			
Summary of evidence	24	Summarise the main findings, including the strength of evidence for each main outcome.	TBA
Strengths and limitations	25	Discuss any important strengths and limitations of the evidence including the benefits of access to IPD and any limitations arising from IPD that were not available.	TBA
Conclusions	26	Provide a general interpretation of the findings in the context of other evidence.	TBA
Implications	A4	Consider relevance to key groups (such as policy makers, service providers and service users). Consider implications for future research.	TBA
Funding			
Funding	27	Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support.	20-21

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2 **A1 – A3 denote new items that are additional to standard PRISMA items. A4 has been created as a result of re-arranging content of the standard PRISMA**
3 **statement to suit the way that systematic review IPD meta-analyses are reported.**
4

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