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Elevated luteinizing hormone despite normal testosterone levels in older men—natural history, risk factors and clinical features

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Summary

Objective: Elevated luteinizing hormone (LH) with normal testosterone (T) suggests compensated dysregulation of the gonadal axis. We describe the natural history, risk factors and clinical parameters associated with the development of high LH (HLH, LH >9.4 U/L) in ageing men with normal T (T ≥ 10.5 nmol/L).

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Design, Patients and Measurements: We conducted a 4.3-year prospective observational study of 3369 community-dwelling European men aged 40-79 years. Participants were classified as follows: incident (i) HLH (n = 101, 5.2%); persistent (p) HLH (n = 128, 6.6%); reverted (r) HLH (n = 46, 2.4%); or persistent normal LH (pNLH, n = 1667, 85.8%). Potential predictors and changes in clinical features associated with iHLH and rHLH were analysed using regression models.

Results: Age >70 years (OR = 4.12 [2.07-8.20]), diabetes (OR = 2.86 [1.42-5.77]), chronic pain (OR = 2.53 [1.34-4.77]), predegree education (OR = 1.79 [1.01-3.20]) and low physical activity (PASE ≤ 78, OR = 2.37 [1.24-4.50]) predicted development of HLH. Younger age (40-49 years, OR = 8.14 [1.35-49.13]) and nonsmoking (OR = 5.39 [1.48-19.65]) predicted recovery from HLH. Men with iHLH developed erectile dysfunction, poor health, cardiovascular disease (CVD) and cancer more frequently than pNLH men. In pHLH men, comorbidities, including CVD, developed more frequently, and cognitive and physical function deteriorated more, than in pNLH men. Men with HLH developed primary hypogonadism more frequently (OR = 15.97 [5.85-43.60]) than NLH men. Men with rHLH experienced a small rise in BMI.

Conclusions: Elevation of LH with normal T is predicted by multiple factors, reverts frequently and is not associated with unequivocal evidence of androgen deficiency. High LH is a biomarker for deteriorating health in aged men who tend to develop primary hypogonadism.

KEYWORDS

ageing, hypogonadism, luteinizing hormone, physical function, testosterone

1 | INTRODUCTION

Ageing is associated with myriad alterations in endocrine functions,[1] some of which may contribute to a decline in health and quality of later life. Elevated luteinizing hormone (LH) with normal testosterone (T) is encountered commonly in ageing men[2] and may present a diagnostic and therapeutic dilemma to the practicing clinician. High LH may signify the onset of dysregulation in the hypothalamic-pituitary-testicular (HPT) axis, whereby compensatory increase in LH is required to mobilize the Leydig cell steroidogenic reserves to maintain normal T production. We have suggested that this may represent a state of "compensated" hypogonadism,[2] where high LH concentration in the face of normal T (HLH) marks an intermediate stage before transitioning towards overt primary hypogonadism (PHG) when testicular reserve eventually becomes exhausted. The rate of transition (progression and reversal) from normal LH (NLH) to HLH and the factors that influence its development in ageing men are important issues that are yet to be explored in prospective studies. Whether men with HLH experience symptoms, functional deficits or morbidity, without the development of a low T, is unclear. In particular, the proportion of men with HLH who exhibit evidence of androgen deficiency is currently unknown. These uncertainties pose important questions regarding the clinical significance of abnormally increased LH in ageing men.[3] The

European Male Ageing Study (EMAS)[4,5] provides an opportunity to help rectify these knowledge gaps through longitudinal observations of unselected men from the general population.

In this study, we aimed to: (i) identify factors predisposing normal LH men to develop high LH and to identify factors, which predict recovery from high LH; (ii) determine the clinical features associated with high LH; and (iii) assess whether men with high LH are at increased risk of developing PHG.

2 | MATERIALS AND METHODS

2.1 | Participants and study design

The study design and recruitment for EMAS have been described previously.[4,5] Briefly, an age-stratified sample of 3369 men aged 40-79 (mean ± SD: 60 ± 11) years was recruited from population registers in eight European centres. Participants completed a postal questionnaire and attended a clinic for further assessments. These men were invited to participate in the follow-up assessment a median of 4.3 years later (range: 3.0-5.7 years). During this period, 168 men died and 407 men were lost to follow-up. Ethical approval for the study was obtained in accordance with local requirements in each centre. All participants provided written informed consent. They completed questionnaires

both at baseline and at follow-up[4,5] about smoking, alcohol consumption and currently treated medical conditions.[3] Anthropometric measurements, Reuben's physical performance test (PPT) and psychomotor processing speed estimation (digit symbol substitution test [DSST]) were performed according to standardized methods.[4,5] Physical, sexual and psychological function was assessed using responses to the Medical Outcome Study (MOS) 36-item Short-Form health survey (SF36), the EMAS Sexual Function Questionnaire and the Beck's Depression Inventory.

2.2 | Hormone measurements

A single fasting morning (before 1000) blood sample was obtained at baseline and at follow-up. T was measured by liquid chromatography-tandem mass spectrometry (LC–MS/MS),[6] with paired baseline and follow-up samples analysed simultaneously. Luteinizing hormone (LH), FSH and SHBG were measured by the E170 platform electro-chemiluminescence immunoassay (Roche Diagnostics, Indianapolis, IN, USA). The Vermeulen formula was used to calculate free (f) T[7] using participant-specific testosterone, SBHG and albumin values. Intra- and interassay coefficients of variation (CV) were as follows: T 4.0% and 5.6%; LH 1.9% and 2.7%; FSH 0.9% and 1.9%; and SHBG 1.9% and 3.2%, respectively. The detection limits for the sex hormones were as follows: T (0.17 nmol/L; 0.05 ng/mL), LH (0.10 U/L), FSH (0.10 U/L) and SHBG (0.35 nmol/L). Insulin was assayed using chemiluminescence (CVs: 3.9% and 5%).

2.3 | Biochemistry/haematology

Standardized measurements were undertaken in laboratories in each centre. Insulin resistance was calculated using the homoeostasis model assessment of insulin resistance (HOMA-IR = fasting insulin [U/mL] × fasting glucose [mmol/L]/22.5).[8]

2.4 | Categorization of participants by LH criteria

Following the criteria described previously,[2] participants were categorized according to LH and T levels: normal LH (NLH, LH ≤ 9.4 U/L and T ≥ 10.5 nmol/L); high LH (HLH, LH > 9.4 U/L and T ≥ 10.5 nmol/L). A LH cut-off of 9.4 U/L was chosen because this was the 97.5 centile value for men aged 40-44 years in the EMAS population.[9] Participants were further categorized by their change in LH status into one of four groups: incident HLH (iHLH) in which men had a normal LH at baseline and an high LH at follow-up; persistent HLH (pHLH) in which men had HLH at both baseline and follow-up; reverted HLH (rHLH) in which men had HLH at baseline and NLH at follow-up; and pNLH in which men had NLH at both baseline and follow-up.

2.5 | Statistical analysis

Baseline and follow-up differences between pNLH, iHLH, pHLH and rHLH men in hormone levels, anthropometrics, biochemistry, sexual, physical and psychological function and health and lifestyle measures were compared between groups using initially the independent samples t test or analyses of variance (ANOVA) for continuous variables and chi-squared tests for categorical variables. Post hoc analyses were performed using Tukey-Kramer tests to allow for multiple pairwise comparisons. Longitudinal within-group differences in parameters were compared using the paired t test for continuous variables and the McNemar test for categorical variables.

Multiple regression models, adjusted for centre as a random effect, were used to account for the hierarchical study design (individuals nested within centres). The relationships between LH status and putative predictors were assessed using multilevel binary logistic regression models, where gonadal status was the outcome, with the pNLH or pHLH group being the referent for the analyses of the potential predictors for iHLH or rHLH, respectively. Nine factors were included as fixed effects: age (40-49, 50-59, 60-69 or ≥70 years), diabetes, BMI (<25, 25-29.9 or ≥30 kg/m^2), smoking status (current, ex or never), alcohol intake (≥5 or <5 days per week), chronic pain, predegree education (education obtained to below a university degree level), partner status (living with a partner or not) and physical activity (PASE ≤ 78 or >78). The factors chosen were not collinear—the variance inflation factors were <3.33.

The relationships between gonadal status and clinical features of high LH were investigated using binary logistic regression models when associations between iHLH, pHLH and rHLH status with sexual, physical and psychological symptoms or medical conditions were assessed, with adjustments for age, comorbidities, BMI, centre, smoking, chronic pain, education and physical activity. Linear regression analysis was used when associations between iHLH, pHLH and rHLH status with functional ratings were assessed, with adjustments for age, comorbidities, BMI, centre, smoking, chronic pain, education and physical activity.

Results from linear regression models are presented as β-coefficients (for standardized variables) with 95% confidence intervals (CI), and results from logistic regression models are presented as odds ratios (OR) with 95% CI. All statistical analyses were conducted using STATA SE version 13 (StataCorp, College Station, TX, USA).

3 | RESULTS

3.1 | Natural history of high LH

Of the 3369 men recruited into EMAS, 1942 men made up the analytical sample after exclusion of those with known pituitary, testicular or adrenal disease (n = 93), men using a medication known to affect the HPT-axis (n = 217), men who had surgical or medical castration (n = 2), men who failed to attend for follow-up assessment (n = 575), men with missing T (n = 77) or LH (n = 45) data and men with a testosterone level <10.5 nmol/L at baseline or follow-up (n = 418, Figure 1). Men with testosterone levels <10.5 nmol/L in EMAS have been described separately.[10,11] Men who died or were lost to follow-up were older, in poorer health, had worse physical and cognitive function and were more likely to smoke (Table S1). This attritional group had also lower fT and higher SHBG and LH levels than the analytical sample.
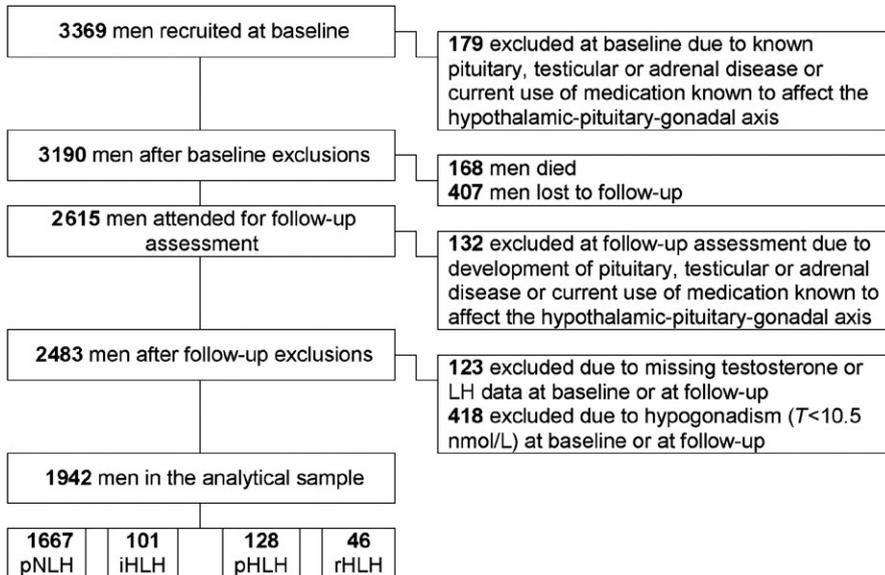
FIGURE 1 Flow chart of Participants. pNLH, persistent normal LH; iHLH, incident high LH; pHLH, persistent high LH; and rHLH, recovery from high LH

Of 305 (9.6%) men who had HLH at baseline, 36 died, 50 were lost to follow-up, 19 developed medical exclusions (eg, started taking HPT-axis affecting drugs), and 7 had no follow-up hormone data. In the remaining 193 men with HLH at baseline with available follow-up data, 128 (66.3%) continued to have HLH at follow-up, 46 (23.8%) reverted to NLH, 15 (7.8%) developed PHG, and 4 (2.1%) developed SHG. The annual incidence of PHG among men with HLH at baseline was 1.8 (1.1-3.0)%/year.

The analytical sample comprised 1667 (85.8%) men with pNLH, 101 (5.2%) with iHLH, 128 (6.6%) with pHLH and 46 (2.4%) rHLH men. The incidence (95% confidence interval) of HLH over the follow-up period was 5.7 (4.7-6.8)%, and the annual incidence rate was 1.3 (1.1-1.6)%/year assuming linearity of HLH development. The recovery rate from HLH to NLH was 26.4 (20.5-33.5)%, and annual recovery rate was 6.8 (5.1-8.9)%/year. The prevalence of HLH at follow-up was 9.5% (n = 229).

3.2 | Characteristics of men who developed high LH

Age, depression (BDI), fasting glucose and PSA were higher, and cognitive function (DSST) and physical activity level (PASE) were lower in iHLH men, at baseline, compared with pNLH men (Table 1). Subjective physical function (SF-36 ratings) and objective physical function (PPT score) were lower in iHLH men at baseline. At follow-up, these earlier differences between the groups persisted, while iHLH men also had lower haemoglobin. The prevalence of poor health and chronic illnesses was higher in the iHLH group than in the pNLH group at both baseline and follow-up (Table 1).

Total T levels were similar in iHLH men and pNLH men at baseline and at follow-up (Table 1). Men with iHLH, compared to pNLH men, had lower fT at baseline (298 ± 94 vs 327 ± 77 pmol/L, $P < .001$) and at follow-up (282 ± 84 vs 313 ± 76 pmol/L, $P < .001$) which may have been due to age-related higher SHBG levels at both time-points. As expected by definition, LH levels were higher in iHLH men than in pNLH men (Figure 2).

3.3 | Characteristics of men who recovered from high LH

Men with rHLH, compared to those with pHLH, were younger, had a lower comorbidity burden and BMI and had higher sexual function, cognitive processing speed and physical function at baseline. These baseline differences persisted at follow-up except for BMI (Table S2).

Men with rHLH had similar T levels at baseline and at follow-up compared to men with pHLH (Table S2). Men with rHLH, however, had higher fT levels, compared to men with pHLH, at baseline (333 ± 90 vs 269 ± 74 pmol/L, $P < .001$) and at follow-up (312 ± 87 vs 246 ± 74 pmol/L, $P < .001$). Luteinizing hormone (LH) levels were lower at baseline and at follow-up in rHLH men compared to pHLH men (Figure 2).

3.4 | Predictors of high LH development and recovery

In men with NLH at baseline, the development of HLH was predicted independently by high age (>70 years, OR 4.12 [2.07-8.20], $P < .001$), diabetes (OR 2.86 [1.42-5.77], $P = .003$), chronic pain (OR 2.53 [1.34-4.77], $P = .004$), education to a below university degree level (OR 1.79 [1.01-3.20], $P = .047$) and low physical activity (PASE ≤ 78, OR 2.37 [1.24-4.50], $P = .009$, Figure 3).

In men with HLH at baseline, recovery from HLH was predicted independently by younger age (40-49 years, OR 8.14 [1.35-49.13], $P = .022$ and 50-59 years, OR 3.38 [1.12-10.19], $P = .030$) and by non-smoker status (OR 5.39 [1.48-19.65], $P = .011$, Figure 3).

3.5 | Symptoms and high LH

At baseline, NLH men who developed HLH did not report a higher frequency of symptoms compared to pNLH men, apart from sadness. Furthermore, they were less likely to report an inability to bend (Figure 4). At follow-up, men with incident HLH were more likely to experience only a worsening of erectile function, but none of the other 8 symptoms.

TABLE 1 Baseline and follow-up characteristics of men with persistently normal luteinizing hormone (LH) and those with incident high LH

Parameter	Baseline			Follow-up		
	pNLH	iHLH	P^a	pNLH	iHLH	P^b
N	1667	101		1667	101	
Age, years	57.2 ± 10.1	63.9 ± 10.9	**<.001**	61.6 ± 10.1***	68.2 ± 10.9***	**<.001**
Predegree education[c], n (%)	—	—	—	1132 (69.2)	79 (81.4)	**.039**
Living with partner, n (%)	—	—	—	1325 (85.0)	77 (81.9)	.420
Smoking, n (%)	333 (20.2)	23 (22.8)	.521	285 (17.7)***	22 (23.4)	*.093*
Frequent alcohol, n (%)	415 (25.0)	22 (21.8)	.758	519 (35.9)***	25 (27.2)	.312
Chronic widespread pain, n (%)	122 (7.6)	14 (14.4)	.145	—	—	—
Poor health, n (%)	308 (18.6)	31 (31.0)	**<.001**	353 (21.9)***	37 (38.1)	**<.001**
≥1 illness, n (%)	593 (35.6)	50 (49.5)	**<.001**	379 (50.2)***	72 (71.3)***	**<.001**
≥2 illnesses, n (%)	216 (16.7)	22 (30.1)	**<.001**	438 (34.5)***	43 (59.7)***	**<.001**
Diabetes, n (%)	73 (4.4)	15 (15.0)	**<.001**	91 (5.6)***	16 (16.5)	**<001**
CVD, n (%)	466 (28.4)	37 (37.0)	**.001**	588 (37.6)***	56 (57.7)***	**<.001**
Cancer, n (%)	59 (3.5)	4 (4.0)	**<.001**	114 (7.2)***	12 (13.2)**	**<.001**
Prostate disease, n (%)	135 (8.2)	5 (5.0)	**.003**	156 (9.7)*	12 (12.4)*	.684
Overall sexual function	22.5 ± 6.4	20.2 ± 7.2	**.002**	21.7 ± 6.7***	18.1 ± 7.6*	**<.001**
SF-36 physical	51.5 ± 7.3	49.7 ± 8.4	**.031**	50.9 ± 8.0**	48.9 ± 8.8	**.044**
Beck's Depression Inventory	6.1 ± 5.9	8.0 ± 6.8	**.003**	6.0 ± 6.4	7.7 ± 6.4	**.003**
SF-36 mental	52.1 ± 8.7	50.3 ± 8.4	**.016**	52.0 ± 9.2	50.4 ± 9.0	**.044**
DSST	29.5 ± 8.1	25.3 ± 8.6	**<.001**	28.7 ± 8.6***	23.3 ± 9.0**	**<.001**
PASE score	211.4 ± 86.4	183.5 ± 95.1	**.005**	186.9 ± 92.7***	165.4 ± 91.8	**.020**
50-ft walk, sec	13.0 ± 2.8	13.5 ± 2.8	**.040**	13.6 ± 2.8***	14.8 ± 3.2***	**<.001**
PPT rating	24.4 ± 2.4	23.8 ± 2.7	**.035**	24.0 ± 2.4***	23.0 ± 2.6***	**.001**
BMI, kg/m^2	27.2 ± 3.8	27.2 ± 4.1	.935	27.3 ± 3.9**	27.5 ± 4.7	.822
FPG, mmol/L	5.4 ± 0.9	5.9 ± 1.5	**.006**	5.4 ± 1.3**	5.7 ± 1.4	**.034**
HOMA-IR	2.7 ± 2.6	3.6 ± 7.5	.647	2.7 ± 2.1*	2.7 ± 2.3*	.590
PSA, ng/mL	1.5 ± 2.1	2.2 ± 3.6	**.003**	2.0 ± 5.2***	2.7 ± 4.3	**.043**
Hb, g/L	150.8 ± 10.4	148.5 ± 11.2	*.053*	150.7 ± 10.8	143.3 ± 16.9*	**<.001**
Total T, nmol/L	18.4 ± 5.4	18.0 ± 5.1	.611	18.1 ± 5.4**	18.2 ± 5.6	.818
Free T, pmol/L	326.7 ± 77.4	298.4 ± 93.7	**<.001**	312.6 ± 76.0***	281.5 ± 84.2*	**<.001**
SHBG, nmol/L	42.9 ± 17.3	48.3 ± 17.0	**<.001**	45.4 ± 18.7***	54.8 ± 21.7***	**<.001**
LH, U/L	5.0 ± 1.7	7.4 ± 1.4	**<.001**	5.0 ± 1.8	11.5 ± 2.4***	**<.001**
FSH, U/L	6.1 ± 3.4	11.2 ± 6.2	**<.001**	6.2 ± 3.5	14.8 ± 8.4***	**<.001**

Data are expressed as mean ± standard deviation for continuous variables or as number (percentage) for binary categorical variables.

NLH, normal luteinizing hormone; HLH, high luteinizing hormone; CVD, cardiovascular disease; SF-36, Short-Form 36 Questionnaire; DSST, Digital Symbol Substitution Test; PASE, Physical Activity Scale for the Elderly; PPT, Physical Performance Test; BMI, Body Mass Index; FPG, fasting plasma glucose concentration; HOMA-IR, HOmeostatic Model of Insulin Resistance; PSA, prostate-specific antigen concentration; Hb, haemoglobin; T, serum testosterone concentration; SHBG, sex hormone-binding globulin concentration; LH, luteinizing hormone concentration; FSH, follicular stimulating hormone concentration.

[a]P-values were calculated using *baseline* parameters and either the independent samples *t* test for continuous variables or chi-squared analyses for categorical variables.

[b]P-values were calculated using *follow-up* parameters and either the independent samples *t* test for continuous variables or chi-squared analyses for categorical variables.

[c]Educated to less than a degree level.

Data differ significantly (*P < .05, **P < .01 and ***P < .001, respectively) from baseline values within the same group when analysed using paired *t* tests (for continuous variables) or the McNemar test (for categorical variables).

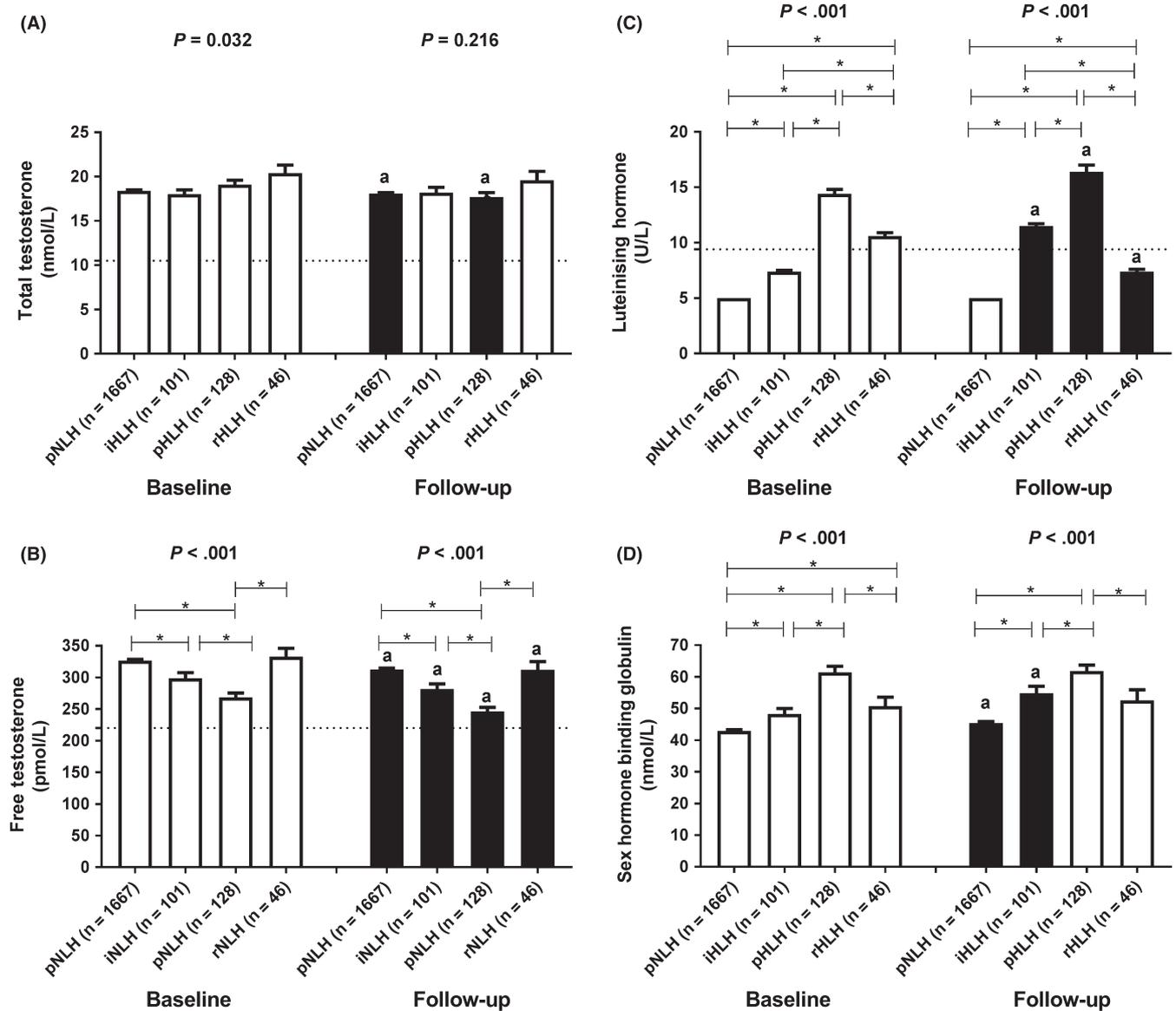P values less than 0.05 have been bolded. P values between 0.05 and 0.1 have been italicized.

FIGURE 2 Sex hormone levels and luteinizing hormone (LH) status at baseline and follow-up for men with persistent normal LH (pNLH), incident HLH (iHLH), persistent HLH (pHLH) and recovery from HLH (rHLH). Baseline and follow-up hormone concentrations are expressed as means (upper limits of bars) and as standard errors of the means (upper limits of the error bars). Data in the groups were compared, and *P*-values were generated, using analyses of variance (ANOVA) and Tukey-Kramer post hoc analyses to permit correction for multiple pairwise comparisons. Solid black bars at follow-up with the letter "a" indicate that follow-up hormone levels in this group differed significantly from baseline hormone levels in the same group when analysed using the paired *t* test. Lines and brackets with stars above bars indicate statistically significant differences between the two groups (*P* < .05). The horizontal dotted lines represent values above or below which are considered abnormal (10.5 nmol/L for total testosterone, 220 pmol/L for calculated free testosterone and 9.4 U/L for luteinizing hormone)

Men with pHLH and pNLH did not differ in symptom frequency at baseline—pHLH men were more likely to develop inability to bend, but none of the other symptoms.

The prevalence and incidence of symptoms were similar between rHLH and pHLH men at baseline or follow-up (Figure 4).

3.6 | Comorbidities, functional ratings and high LH

At baseline, men with iHLH were more likely to have diabetes, insulin resistance, lower haemoglobin and lower mood (SF-36 mental) than pNLH men (Table 2). At follow-up, men with iHLH experienced a greater rise in time taken to walk 50 feet, a greater fall in haemoglobin and were more likely to develop poor health, cardiovascular disease and cancer than men with pNLH.

At baseline, men with pHLH were more likely to have diabetes and cancer, lower cognitive processing speed (DSST), higher insulin resistance and lower haemoglobin levels than men with pNLH. During follow-up, men with pHLH, compared to men with pNLH, were more likely to develop comorbidity, including CVD, while physical function (PPT rating) and cognitive processing speed worsened more (Table 2).
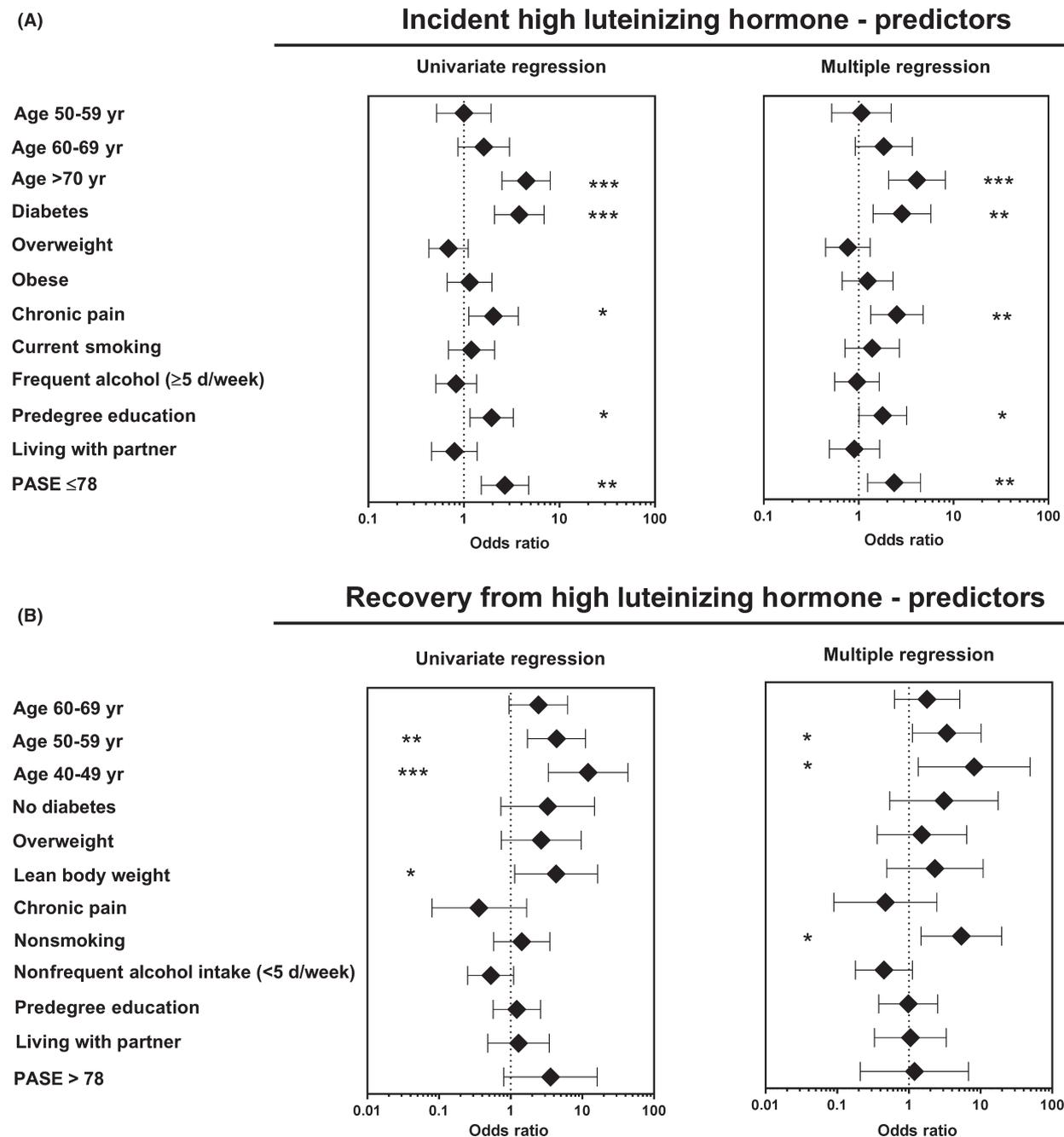
(A)

Incident high luteinizing hormone - predictors

(B)

Recovery from high luteinizing hormone - predictors

FIGURE 3 Potential Risk Factors for development of, and recovery from, high luteinizing hormone (LH). Data are expressed as odds ratio (symbol) ±95% confidence interval (error bars). In the left panels, odds ratios and *P*-values were determined using single independent variables and binary logistic regression analyses (unadjusted/univariate). In the right panels, odds ratios and *P*-values were determined using multiple binary logistic regression analysis including all the potential risk factors listed in the same model. *P < .05; **P < .01; ***P < .001

3.7 | Progression from high LH to primary hypogonadism (PHG)

Men with HLH at baseline were more likely to develop PHG in both unadjusted analysis (OR 21.77 [8.76-54.12], P < .001) and in fully adjusted analysis (OR 15.10 [5.54-41.20], P < .001) than were NLH men. The annual rate of progression from HLH to PHG was 1.8%/year [1.1-3.0] [total progression rate was 7.8% (4.8-12.4)].

Men who transitioned from HLH to PHG, compared to pHLH men, had lower T (13.5 ± 2.5 vs 19.1 ± 5.5 nmol/L, P < .001) and fT levels (189 ± 57 vs 269 ± 74 pmol/L, P < .001) at baseline, while LH (20.4 ± 15.5 vs 14.4 ± 4.8 U/L, P = .306) and SHBG levels (68.4 ± 50.1 vs 61.4 ± 21.5 nmol/L, P = .388) were similar. The transition from HLH to PHG was underlined by noteworthy declines in both T (−4.8 ± 3.5 nmol/L and −34.2% ± 21.2%) and fT (−58 ± 40 pmol/L and −33.3% ± 22.1%), even though T and fT levels were already lower at both baseline and follow-up compared to other groups.
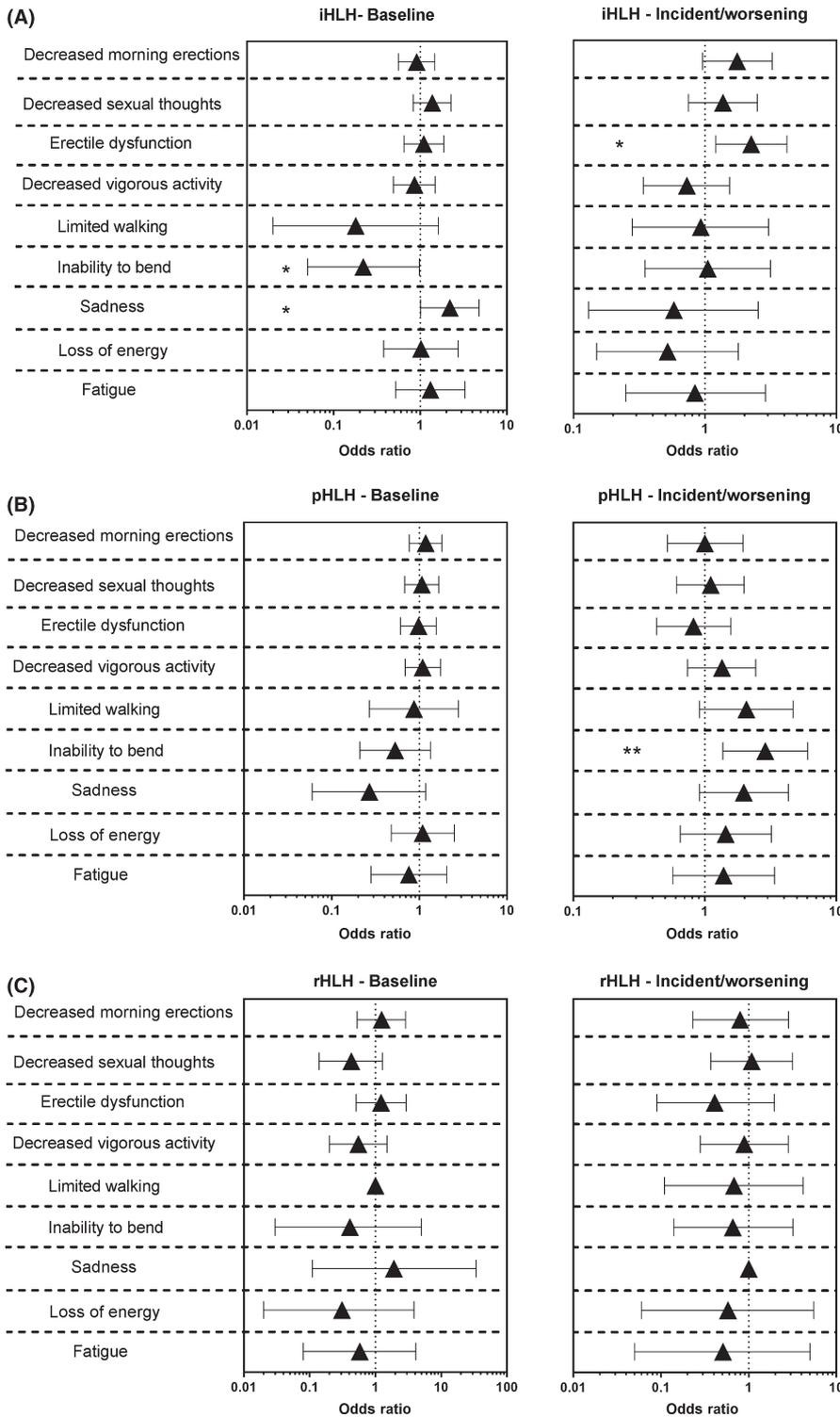
FIGURE 4 Relationships between Symptoms and High luteinizing hormone (LH). Data are expressed as odds ratios (▲) ±95% confidence intervals (error bars). Odds ratios and *P*-values were determined using regression analyses. Data from the incident high LH (iHLH) and persistent high LH (pHLH) groups were compared to those from the referent group of persistent normal LH (pNLH). Recovery from high LH (rHLH) data were compared to those of pHLH men. The statistical analysis was performed with adjustment for age, comorbidity, body mass index, centre, chronic pain, education, smoking and physical activity. The left panels show the odds ratios for the prevalence of symptoms at baseline. The right panels show the odds ratios for the development/worsening of symptoms. *, *P* < .05; **, *P* < .01

4 | DISCUSSION

In this prospective and longitudinal analysis of 3369 community-dwelling men, we have described, for the first time, the natural history and clinical phenotype of men who develop elevated LH (and normal T), have identified risk factors predisposing to the development of HLH and documented the likelihood of progression to PHG and recovery from HLH.

Men who go onto develop HLH, compared to men who do not, experience a greater fall in haemoglobin and walking speed with increased risks of developing CVD and cancer. These findings, together with the persistently normal mean T of ≥18 nmol/L and a lack of decreased libido and morning erections, suggest that the clinical correlates of iHLH are not typical of hypogonadism, but rather represent those associated with poor or deteriorating health. This is reinforced further by our findings showing that pHLH men have lower levels of

TABLE 2 Comorbidities, functional ratings and elevated luteinizing hormone

Parameter	Incident HLH (n = 101)		Persistent HLH (n = 128)		Recovery from HLH (n = 46)	
	Baseline	Change[a]	Baseline	Change[a]	Baseline	Change[a]
Poor health, n (%)	1.29 (0.76, 2.18)	**1.98 (1.01, 3.90)***	1.39 (0.86, 2.22)	1.60 (0.84, 3.03)	0.74 (0.26, 2.09)	0.56 (0.13, 2.37)
≥1 illness, n (%)	1.10 (0.68, 1.78)	1.75 (0.92, 3.31)	**1.76 (1.12, 2.76)***	**2.02 (1.03, 3.98)***	0.49 (0.21, 1.14)	0.52 (0.14, 1.85)
≥2 illnesses, n (%)	0.99 (0.52, 1.86)	1.85 (0.84, 4.06)	**1.85 (1.05, 3.26)***	2.09 (0.94, 4.66)	0.86 (0.30, 2.48)	0.78 (0.07, 8.42)
Diabetes, n (%)	**2.62 (1.34, 5.14)*****	0.35 (0.05, 2.73)	**2.13 (1.12, 4.08)***	0.36 (0.05, 2.81)	0.36 (0.07, 1.94)	12.75 (0.49, 332.44)
CVD, n (%)	0.89 (0.54, 1.46)	**2.09 (1.12, 3.90)***	1.37 (0.88, 2.12)	**2.58 (1.33, 5.00)****	0.80 (0.33, 1.95)	0.92 (0.29, 2.87)
Cancer, n (%)	0.67 (0.20, 2.25)	**2.77 (1.29, 5.97)***	**2.06 (1.05, 4.05)***	0.88 (0.33, 2.34)	1.28 (0.34, 4.76)	1.74 (0.33, 9.22)
Prostate disease, n (%)	**0.27 (0.09, 0.77)***	1.18 (0.53, 2.66)	1.21 (0.70, 2.09)	0.34 (0.10, 1.14)	0.52 (0.13, 2.09)	5.54 (0.70, 44.16)
Overall sexual function	−0.03 (−0.08, 0.02)	−0.02 (−0.08, 0.04)	−0.02 (−0.07, 0.02)	−0.00 (−0.06, 0.06)	0.05 (−0.11, 0.21)	−0.01 (−0.24, 0.23)
SF-36 physical	0.01 (−0.03, 0.06)	−0.03 (−0.08, 0.02)	−0.00 (−0.05, 0.04)	−0.05 (−0.10, 0.01)	−0.04 (−0.19, 0.12)	−0.02 (−0.19, 0.16)
Beck's Depression Inventory	0.03 (−0.01, 0.08)	0.03 (−0.02, 0.09)	0.04 (−0.01, 0.09)	−0.02 (−0.07, 0.04)	−0.09 (−0.26, 0.07)	0.11 (−0.06, 0.28)
SF-36 mental	**−0.05 (−0.10, −0.00)***	−0.00 (−0.05, 0.05)	−0.01 (−0.06, 0.04)	−0.02 (−0.08, 0.03)	0.03 (−0.14, 0.19)	0.02 (−0.15, 0.20)
DSST	−0.03 (−0.07, 0.01)	−0.02 (−0.07, 0.03)	**−0.07 (−0.11, −0.02)****	**−0.05 (−0.10, −0.00)***	0.08 (−0.06, 0.21)	0.10 (−0.07, 0.26)
PASE score	−0.03 (−0.08, 0.01)	0.02 (−0.03, 0.08)	−0.04 (−0.09, 0.01)	−0.04 (−0.10, 0.01)	0.00 (−0.15, 0.15)	0.04 (−0.14, 0.23)
50-ft walk, seconds	−0.01 (−0.06, 0.03)	**0.05 (0.01, 0.10)***	−0.00 (−0.05, 0.04)	0.03 (−0.01, 0.08)	−0.15 (−0.30, 0.00)	0.10 (−0.06, 0.27)
PPT rating	0.01 (−0.04, 0.05)	−0.01 (−0.06, 0.04)	0.00 (−0.04, 0.05)	**−0.09 (−0.14, −0.04)****	−0.05 (−0.11, 0.20)	0.03 (−0.14, 0.20)
BMI, kg/m²	−0.01 (−0.05, 0.04)	−0.01 (−0.06, 0.04)	−0.04 (−0.09, 0.01)	0.01 (−0.04, 0.06)	−0.10 (−0.26, 0.06)	**0.21 (0.05, 0.36)***
HOMA-IR	**0.07 (0.02, 0.11)****	−0.02 (−0.07, 0.04)	**0.09 (0.04, 0.14)*****	0.01 (−0.04, 0.07)	−0.04 (−0.20, 0.12)	0.11 (−0.07, 0.29)
Hb, g/L	**−0.05 (−0.10, −0.00)***	**−0.06 (−0.11, −0.01)***	**−0.10 (−0.15, −0.05)*****	0.04 (−0.01, 0.10)	0.10 (−0.07, 0.26)	−0.15 (−0.33, 0.03)

Data are expressed as odds ratio (95% confidence interval) for binary categorical variables or as regression co-efficient (95% confidence interval) for continuous variables.

Data from men with incident or persistent HLH were compared to those from men with persistently normal LH levels. Data from men with recovery from HLH were compared to those from men with persistent HLH. All relationships are adjusted for age, comorbidity, body mass index, centre, chronic pain, education, smoking and physical activity.

HLH, high luteinizing hormone; CVD, cardiovascular disease; SF-36, Short-Form 36 Questionnaire; DSST, Digital Symbol Substitution Test; PASE, Physical Activity Scale for the Elderly; PPT, Physical Performance Test; BMI, Body Mass Index; HOMA-IR, HOmeostatic Model of Insulin Resistance; Hb, haemoglobin.

Values with an associated probability value less than 0.05 have been bolded.

[a]Incidence of comorbidity or percentage change from baseline for functional ratings.

*P < .05.

**P < .01.

***P < .001.

haemoglobin and cognitive function (DSST) at baseline, greater worsening of DSST and physical functioning over time and increased co-morbidity at baseline (diabetes and cancer) and follow-up (CVD).

We have hypothesized previously that compensated hypogonadism (here referred to as HLH) may be a transitional state, which presages the development of overt PHG.[2] We show now that the development of HLH is predicted independently by age >70 years, diabetes, chronic pain, predegree education and low physical activity. The longitudinal association between high age and iHLH reinforces our previous cross-sectional results.[2] This association, together with the novel identification of diabetes, pain and physical activity as factors that predispose to the development of HLH, suggests that HLH can be regarded as a feature of functional ageing. The possible link between socio-economic factors (education to a less than university degree level) and the development of HLH presents a fresh perspective on the predisposition to adverse outcomes of endocrine ageing. It is recognized that people with better educational attainment are healthier and live longer[12]—it may be that Leydig cell functional reserve plays a mediating role in this relationship. Interestingly, obesity is not a predictor of HLH, yet the occurrence of HLH appears to be predicted by diabetes. In this respect, HLH is more closely linked to PHG[11] than to SHG which is related to obesity and not to age or chronic illness.[10] This highlights the different underlying pathophysiological mechanisms contributing to the decline in T in older men as well as their distinct clinical implications.

It follows that a vicious circle may exist for men with HLH—factors associated with accelerated functional ageing (diabetes, chronic pain and physical inactivity) predispose to HLH development and HLH, in turn, predisposes to further functional decline (decrease in haemoglobin, physical function and cognitive function as well as development of CVD).

With a baseline prevalence of HLH in EMAS of 9.4%,[2] an incidence rate of 1.3%/year and recovery rate of 6.8%/year, HLH appears to be a relatively common but reversible condition in the general population. Recovery from HLH was associated with younger age and being a non-smoker. It is plausible, that, as compared to pHLH men, the younger rHLH men might have a higher reserve of testicular steroidogenic function or Leydig cell population, which allowed them to compensate for potential insults to Leydig cells due to disease. Less likely is the possibility that younger and healthier men had greater LH pulsatility (vide infra) increasing their chance of being classified as HLH at baseline due to a blood sample being obtained during an LH pulse. The observation that nonsmoking is a predictor for the recovery from HLH is in agreement with our baseline cross-sectional findings showing that smoking status is related to HLH.[2] The higher SHBG levels observed in smokers might explain this finding,[13] although the exact mechanism remains unclear. Except for minor changes in BMI, none of the androgen-sensitive endpoints or medical conditions assessed within our study were associated or changed with rHLH. This supports the view that HLH is not a hypogonadal condition although a significant proportion of HLH men will go on to develop PHG within the ensuing 5 years.

The HPT-axis is regulated tightly in older as in young men,[14] and elevated LH is highly responsive to age-related deficits in Leydig cell mass[15] and function.[16] Impaired testicular response to LH can be caused by exposure to cytokines,[17,18] arising from chronic low-grade inflammation,[19] which is common in ageing.[20] Testicular failure with elevated gonadotropins is also associated with chronic diseases of ageing including cancer,[21] diabetes,[22] renal and liver failure and COPD.[23] In addition, elevated LH, independent of testicular failure, has been associated with increased all-cause and cancer-specific mortality.[24] Elevated LH can be therefore considered a biomarker of poor health and subclinical chronic diseases. Accordingly, iHLH is predicted by the presence of diabetes, and iHLH men are at risk of developing CVD and cancer.

4.1 | Strengths and limitations

This prospective study provided an opportunity to investigate the temporal relationships between the earliest ageing-related changes in HPT-axis function and their clinical correlates. The strengths of the study include the longitudinal follow-up of a large number of unselected participants from the general population and the breadth of the phenotypic data collected by standardized validated methods between the phases of the study. T was measured by LC–MS/MS with paired baseline and follow-up samples analysed simultaneously. Limitations in EMAS have been described previously.[4,5] The follow-up period of 4.3 (range: 3.0-5.7) years may be a relatively short time in which to capture more protracted changes in signs and symptoms of hypogonadism. A relatively small number of men developed HLH—this is unavoidable given the relatively low incidence of the condition which has not been previously described. However, the ability to identify significant and consistent associations (albeit with wide confidence intervals) despite the relatively small numbers of cases supports the validity of our findings and conclusions. At both study phases, a single LH and T measurement only was available to categorize gonadal status. This may have introduced errors in classification although the consistency of higher LH between baseline and follow-up and the parallel changes in FSH add confidence to our results. Multiple blood sample collection is impractical in large epidemiological surveys[25,26] such as ours. Several studies have confirmed that T levels within the same individual do not fluctuate significantly when measured serially over several months.[27-30] Similarly, the diurnal variation in LH levels is markedly less prominent, if not absent, in older men.[31] In our analytical sample, the coefficients of correlation between baseline and follow-up T and LH levels were 0.72 (P < .001) and 0.80 (P < .001), respectively. It is unlikely, therefore, that single hormone determination in the present study would have introduced substantial misclassification of gonadal status. The fact that the vast majority of EMAS participants had a normal LH at baseline and at follow-up and the parallel changes in FSH attest to this.

4.2 | Conclusions and clinical implications

Age greater than 70 years, diabetes, chronic pain, predegree education and low physical activity predispose men to the development of high LH, which may be reversible in younger men. High LH, with normal T, can be regarded as a sensitive biomarker of poor health and a

risk factor for developing PHG. Incident HLH is not associated with unequivocal evidence of androgen deficiency. Even if HLH persists for several years, the emergent physical and cognitive impairments are not typical features of hypogonadism, but rather reflect deteriorating health during ageing.

In clinical practice, men with elevated LH and normal T should be followed up for their general as well as endocrine reproductive health, but there is no indication for T replacement therapy unless T falls into the hypogonadal range and more features of androgen deficiency appear (ie, progression to PHG).

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CONFLICT OF INTEREST

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