Development of and Recovery from Secondary Hypogonadism in Aging Men: Prospective Results from the EMAS

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Context: Secondary hypogonadism is common in aging men; its natural history and predisposing factors are unclear.

Objectives: The objectives were 1) to identify factors that predispose eugonadal men (T $\geq$ 10.5 nmol/L) to develop biochemical secondary hypogonadism (T $<$ 10.5 nmol/L; LH $\leq$ 9.4 U/L) and secondary hypogonadal men to recover to eugonadism; and 2) to characterize clinical features associated with these transitions.

Design: The study was designed as a prospective observational general population cohort survey.

Setting: The setting was clinical research centers.

Participants: The participants were 3369 community-dwelling men aged 40–79 years in eight European centers.

Intervention: Interventions included observational follow-up of 4.3 years.

Main Outcome Measure: Subjects were categorized according to change/no change in biochemical gonadal status during follow-up as follows: persistent eugonadal (n = 1909), incident secondary hypogonadal (n = 140), persistent secondary hypogonadal (n = 123), and recovered from secondary hypogonadism to eugonadism (n = 96). Baseline predictors and changes in clinical features associated with incident secondary hypogonadism and recovery from secondary hypogonadism were analyzed by regression models.

Results: The incidence of secondary hypogonadism was 155.9/10 000/year, whereas 42.9% of men with secondary hypogonadism recovered to eugonadism. Incident secondary hypogonadism was predicted by obesity (body mass index $\geq$ 30 kg/m^2; odds ratio [OR] = 2.86 [95% confidence interval, 1.67; 4.90]; *P* $<$ .0001), weight gain (OR = 1.79 [1.15; 2.80]; *P* = .011), and increased waist circumference (OR = 1.73 [1.07; 2.81], *P* = .026; and OR = 2.64 [1.66; 4.21], *P* $<$ .0001, for waist circumference 94–102 and $\geq$102 cm, respectively). Incident secondary hypogonadal men experienced new/worsening sexual symptoms (low libido, erectile dysfunction, and infrequent spontaneous erections). Recovery from secondary hypogonadism was predicted by nonobesity (OR = 2.28 [1.21; 4.31]; *P* = .011), weight loss (OR = 2.24 [1.04; 4.85]; *P* = .042), normal waist circumference (OR = 1.93 [1.01; 3.70]; *P* = .048), younger age ($<$ 60 y; OR = 2.32 [1.12; 4.82]; *P* = .024), and higher education (OR = 2.11 [1.05; 4.26]; *P* = .037), but symptoms did not show significant concurrent improvement.

Conclusion: Obesity-related metabolic and lifestyle factors predispose older men to the development of secondary hypogonadism, which is frequently reversible with weight loss. ***(J Clin Endocrinol Metab* 100: 3172–3182, 2015)**

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Abbreviations: BDI, Beck Depression Index; BMI, body mass index; CI, confidence interval; DSST, digit symbol substitution test; EUG, eugonadism; HDL, high-density lipoprotein; HG, hypogonadism; HOMA-IR, homeostasis model assessment of insulin resistance; isHG, incident sHG; MetS, metabolic syndrome; OR, odds ratio; PASE, Physical Activity Scale for the Elderly; pEUG, persistent EUG; PPT, physical performance test; psHG, persistent sHG; rsHG, recovery from sHG; SF-36, 36-item Short-Form Health Survey; sHG, secondary HG; WC, waist circumference.

After the third decade, T decreases in men by 0.4–2% per year (1). Besides aging, other risk factors, particularly obesity, contribute substantially to the T decline irrespective of age (1, 2). There is also evidence suggesting that low T can promote fat accumulation (3) and suggesting a bidirectional relationship between obesity and low T. Longitudinal data from the European Male Ageing Study (EMAS) showed that weight gain was progressively associated with a decline in T levels without a concomitant change in LH (4), compatible with secondary hypogonadism (sHG). Furthermore, weight loss was proportionately associated with increases in T (4), suggesting that sHG is potentially reversible.

sHG accounts for more than 50% of men with low T in the general population (5) and in patients with sexual dysfunction (6). To better understand the natural history and clinical significance of sHG, it is important to further investigate longitudinally the role of obesity, relative to other potential risk factors, in predicting the development of and recovery from sHG.

Symptoms of androgen deficiency in the presence of low T provide the diagnostic cornerstone of the syndrome of hypogonadism (7). Late-onset hypogonadism has been stringently defined by us as subnormal T associated with three sexual symptoms (5, 8). However, the cross-sectional association between low T and symptoms was attenuated after adjusting for body mass index (BMI) and comorbidities (5), underlining the multicausal origin of putative symptoms of hypogonadism in aging men. Moreover, obesity, independent of T, is associated with sexual (9) and psychological symptoms (10) as well as impaired physical activity (11). Confirming the appearance of these symptoms with the development of biochemical hypogonadism and/or their resolution after recovery to eugonadism (EUG) would support their relevance as specific clinical markers of androgen deficiency, important in the diagnostic workup of men with low T.

The aim of the study was to identify predictors of, and symptoms associated with, incident sHG (isHG) and recovery from sHG (rsHG) in middle-aged and older men from the general population.

Subjects and Methods

Participants and study design

The EMAS design and methods have been previously described (12, 13). Briefly, an age-stratified sample of 3369 men aged 40–79 (mean ± SD, 60 ± 11) years was recruited from population registers in eight European centers: Manchester (United Kingdom), Leuven (Belgium), Malmö (Sweden), Tartu (Estonia), Lodz (Poland), Szeged (Hungary), Florence (Italy) and Santiago de Compostela (Spain). Participants attended research clinics at baseline and 4.3 years later (range, 3.0–5.7 y) for follow-up assessments (12, 13). During this period, 193 men died, 334 were lost to follow-up, and 106 were institutionalized or became too frail. Ethical approval for the study was obtained according to institutional requirements in each center. All participants provided written, informed consent. They completed questionnaires at both baseline and follow-up (12, 13) about smoking, alcohol consumption, and currently treated comorbidities (1). Anthropometric measurements, Reuben's physical performance test (PPT), and psychomotor processing speed (digit symbol substitution test [DSST]) were performed according to standardized methods (12, 13). Physical, sexual, and psychological symptoms were determined from responses to the Medical Outcomes Study (MOS) 36-item Short-Form health survey (SF-36), the EMAS Sexual Function Questionnaire, and the Beck Depression Inventory (BDI), respectively.

Hormone measurements

Single, fasting morning (before 10 AM) venous blood samples were obtained at baseline and follow-up. T was measured by liquid chromatography–tandem mass spectrometry, with paired baseline and follow-up samples analyzed simultaneously. LH, FSH, and SHBG were measured by the E170 platform electrochemiluminescence immunoassay (Roche Diagnostics). Free T was calculated using the Vermeulen formula (14). Intra- and interassay coefficients of variation (CVs) were: T, 4.0 and 5.6%; SHBG, 1.7 and 3.2%; LH, 1.9 and 3.0%; and FSH, 1.8 and 5.3%, respectively. The lower limit of total T measurement was 0.17 nmol/L (0.05 ng/mL). Insulin was assayed using chemiluminescence (coefficients of variation, 3.9 and 5%). Biochemistry and hematology parameters were performed with standardized measurements, undertaken in hospital laboratories in each center. Insulin resistance was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR = fasting insulin [U/mL] × fasting glucose [mmol/L]/22.5) (15).

Gonadal status

Participants with T ≥ 10.5 nmol/L were defined as EUG; when T < 10.5 nmol/L and LH < 9.4 U/L, they were defined as having sHG (5). Subjects were further categorized by their change in gonadal status into:

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1) persistent EUG (pEUG)—EUG at baseline and follow-up; 2) incident sHG (isHG)—EUG at baseline and sHG at follow-up; 3) persistent sHG (psHG)—sHG at baseline and follow-up; and 4) rsHG—sHG at baseline and EUG at follow-up.

Statistical analysis

Baseline differences between isHG and pEUG and between rsHG and psHG in hormone levels, anthropometrics, biochemistry, symptoms, and health and lifestyle measures were initially evaluated by Student's *t* test for continuous variables and χ^2 test for categorical variables.

Multiple regression models, adjusted for center as a random effect, were used to account for the hierarchical study design (individuals nested within center). The relationships between gonadal status and putative predictors were assessed using multilevel binary logistic regression models, where gonadal status was the outcome, with the pEUG or psHG group being the referent for the analyses of predictors of isHG or rsHG, respectively. Nine factors were included as fixed-effect predictors: age, smoking status (current smoker, yes/no), alcohol intake (alcohol consumption for ≥5 d/wk vs less), education level (low [compulsory education only], medium [noncompulsory education below university level], or high [university education]), Physical Activity Scale for the Elderly (PASE) score (≤78 vs >78), chronic widespread pain (yes/no), marital status (no partner, having a partner but not living together, or having a partner and living together), comorbidity (presence/absence of at least one self-reported disorder), BMI (<25, 25–29.9, and ≥30 kg/m^2), and waist circumference (WC) (<94, 94–101.9, and ≥102 cm).

The relationship between gonadal status and clinical features of hypogonadism was investigated using binary logistic regression models with symptoms dichotomized as stable or new/worsened as the outcome when assessing outcomes of isHG, and as stable or resolved/improved when assessing outcomes of rsHG. A symptom was defined as "new" when absent at baseline and present at follow-up and as "worsened" when present at baseline but with a lower severity grading than at follow-up. A symptom was defined as "resolved" when present at baseline and absent at follow-up and as "improved" when present at follow-up with a lower severity grading than at baseline.

Differences in clinical characteristics between isHG and pEUG or between rsHG and psHG at baseline and changes over time were investigated by multiple logistic regression models adjusted for age (as a continuous variable), center, baseline BMI (as a continuous variable), presence of at least one comorbidity at baseline, smoking, and alcohol intake.

Linear regression models were used to evaluate the association between isHG or rsHG and baseline levels or percentage change of metabolic and hematological parameters, expressed as continuous variables.

For isHG predictor analysis, weight gain was defined as ≥5% increase of the baseline value. In the rsHG predictor analysis, weight loss was defined as ≥5% decrease of the baseline value.

Results from logistic regression models are presented as odds ratios (ORs) and 95% confidence intervals (CIs), and results from linear regression models are presented as β coefficients with 95% CIs. All statistical analyses were conducted using SPSS for Windows 20.1 (IBM).

Results

Natural history of sHG

Of the 3369 men that participated in the EMAS (Figure 1), 193 were excluded at baseline because of medical con-

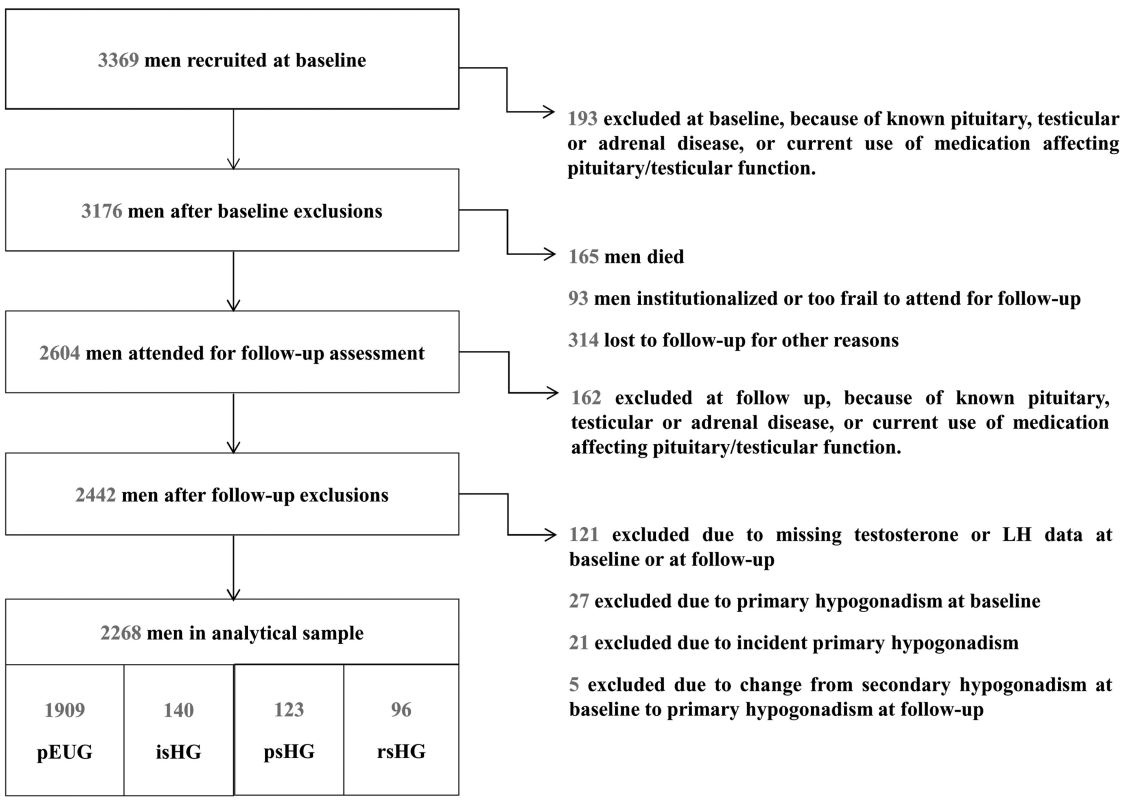

Figure 1. Study flowchart showing exclusion of subjects and distribution of study sample by gonadal status.

Table 1. Characteristics of the Sample at Baseline and Follow-Up Categorized Into Four Groups by Gonadal Status: pEUG (n = 1909), isHG (n = 140), psHG (n = 123), rsHG Subjects (n = 96)

	Baseline			Follow-Up		
	pEUG	**isHG**	***P***	**pEUG**	**isHG**	***P***
Age, y	58.3 ± 10.5	57.2 ± 10.4	.251			
Total T, nmol/L	**18.4 ± 5.4**	**12.7 ± 2.0**	**.000**	**18.1 ± 5.4****	**8.8 ± 1.7****	**.000**
Calculated free T, pmol/L	**322.3 ± 80.2**	**272.2 ± 48.1**	**.000**	**369.3 ± 180.9****	**227.3 ± 117.6****	**.000**
SHBG, nmol/L	**44.5 ± 18.2**	**29.8 ± 10.4**	**.000**	**47.0 ± 19.5****	**28.9 ± 11.5**	**.000**
LH, U/L	**5.8 ± 3.2**	**4.7 ± 2.0**	**.000**	**6.1 ± 3.9****	**4.4 ± 1.8***	**.000**
FSH, U/L[a]	**5.9 [2.0–24.6]**	**5.0 [2.0–17.2]**	**.005**	**5.9 [2.0–26.6]****	**5.0 [1.7–17.6]**	**.000**
Hemoglobin, g/L	150.4 ± 10.4	149.6 ± 9.8	.342	**150.1 ± 11.4**	**146.7 ± 12.4***	**.003**
Total cholesterol, mmol/L	5.6 ± 1.0	5.7 ± 1.1	.116	5.3 ± 1.0****	5.1 ± 1.1****	.073
HDL-cholesterol, mmol/L[a]	**1.4 [0.9–2.3]**	**1.3 [0.8–2.2]**	**.000**	**1.3 [0.8–2.3]****	**1.2 [0.7–2.5]****	**.000**
Triglycerides, mmol/L[a]	**1.2 [0.5–3.8]**	**1.5 [0.5–5.3]**	**.000**	**1.2 [0.5–3.7]**	**1.5 [0.5–6.5]**	**.000**
LDL-cholesterol, mmol/L	3.5 ± 0.9	3.6 ± 0.9	.163	**3.3 ± 1.0****	**3.1 ± 1.1****	**.035**
Glucose, mmol/L[a]	**5.3 [4.3–8.6]**	**5.4 [4.3–7.7]**	**.039**	**5.2 [4.1–8.9]***	**5.6 [3.9–9.3]**	**.002**
HOMA-IR[a]	**2.0 [0.6-10.0]**	**2.7 [0.9-18.6]**	**.000**	**1.5 [0.0–7.1]****	**2.3 [0.6-16.8]**	**.000**
MetS, %	**18.3**	**36.0**	**.000**	**22.1****	**52.7****	**.000**
Weight, kg	**82.5 ± 13.1**	**87.9 ± 13.8**	**.000**	**82.4 ± 13.4***	**90.7 ± 16.6****	**.000**
BMI, kg/m^2	**27.1 ± 3.8**	**29.2 ± 3.8**	**.000**	**27.2 ± 3.9*****	**30.2 ± 4.7****	**.000**
WC, cm	**96.7 ± 10.4**	**102.1 ± 9.5**	**.000**	**98.0 ± 11.0****	**105.3 ± 12.7****	**.000**
PASE score	207.3 ± 87.7	200.1 ± 88.0	.371	183.1 ± 93.5****	167.1 ± 96.4**	.060
≥1 comorbidity, %	**37.8**	**48.6**	**.012**	**52.9****	**70.8****	**.000**
Frequent alcohol use, %	24.9	20.7	.263	35.4****	36.6****	.790
Current smoker, %	20.6	17.3	.352	**18.2****	**10.8**	**.032**
SF-36 physical function	51.1 ± 7.5	51.9 ± 7.7	.283	50.6 ± 8.2***	49.3 ± 9.2****	.144
SF-36 mental function	52.0 ± 8.7	53.0 ± 7.9	.208	52.0 ± 9.1	52.1 ± 8.6	.930
BDI	6.3 ± 5.9	6.5 ± 5.8	.633	6.2 ± 6.2	6.4 ± 6.6	.679
PPT rating	24.3 ± 2.4	24.5 ± 2.5	.323	23.8 ± 2.5****	23.4 ± 2.6****	.054
DSST	28.9 ± 8.4	29.1 ± 8.7	.765	28.02 ± 8.9****	27.2 ± 9.9****	.374

Abbreviation: LDL, low-density lipoprotein. *P* values refer to comparisons between pEUG and isHG subjects or between psHG and rsHG subjects, evaluated by unpaired *t* test for continuous variable and χ^2 test for categorical variables. Asterisks refer to comparison between baseline and follow-up in the same group (pEUG, isHG, psHG or rsHG), evaluated by paired *t* test for continuous variables and McNemar's test for categorical variables. *, $P < .05$; **, $P < .01$; ***, $P < .001$; ****, $P < .0001$. Continuous variables were expressed as mean ± SD, when normally distributed or median [95% CI], when non-normally distributed. Categorical variables were expressed as percentages. Data reported in bold highlight significant differences.

[a] Paired and unpaired *t* tests have been performed using natural log-transformed data for normalizing skewed distributed variables.

ditions (known pituitary-testicular diseases and medications affecting T); 165 died during the follow-up period; 93 were institutionalized or too frail to attend for follow-up; and 314 were lost to follow-up for other reasons. Another 162 were excluded at follow-up because of medical conditions/medications, and 121 were excluded due to missing total T and/or LH levels at baseline and/or follow-up. Among the baseline attendees, the prevalence of sHG was 10.0% (n = 318). In this sHG group, mortality and lost-to-follow-up rates were 8.2 and 11.3%, compared to the entire cohort's rates of 5.2 and 9.9%, respectively. In the analytical sample of 2268 men, 1909 were pEUG, 140 isHG, 123 psHG, and 96 rsHG (Figure 1). The prevalence of sHG at follow-up was 11.0%, and the incidence of sHG from EUG was 6.28% in 4.3 years, or 155.9 per 10 000 per year, or 1.6% per annum. The recovery rate from sHG to EUG was 30.2% (96 of 318) or 42.9% (96 of 224, excluding 94 subjects not attending the second assessment) in 4.3 years.

Compared with the analytical sample, men who died, who were institutionalized, or who were too frail to attend were older; had lower free T and higher SHBG and gonadotropins, but not significantly different total T levels; and reported more diabetes mellitus and cardiovascular diseases and worse physical performance (Supplemental Table 1). Conversely, subjects who were lost to follow-up for other reasons were similar to the analytical group, except for a higher prevalence of smoking and metabolic syndrome (MetS) and lower psychomotor processing speed.

Characteristics of isHG

Lower mean total T, free T, SHBG, LH, and FSH levels were already apparent in isHG men compared to pEUG men at baseline; these differences were replicated and amplified at follow-up (Table 1). isHG men were overweight/obese at baseline, with higher prevalence of comorbidities and MetS; these factors increased further at follow-up. isHG men also showed differences in baseline and follow-up metabolic pro-

Table 1. (Continued)

	Baseline			Follow-Up		
	psHG	rsHG	*P*	psHG	rsHG	*P*
Age, y	57.6 ± 10.6	55.8 ± 8.6	.165			
Total T, nmol/L	**8.3 ± 1.8**	**9.2 ± 1.0**	**.000**	**8.0 ± 2.0**	**13.3 ± 2.9****	**.000**
Calculated free T, pmol/L	198.0 ± 49.5	202.4 ± 37.5	.455	**240.7 ± 156.2*****	**329.7 ± 161.6****	**.000**
SHBG, nmol/L	**22.7 ± 8.9**	**26.1 ± 7.7**	**.004**	**24.5 ± 9.2****	**31.9 ± 10.0****	**.000**
LH, U/L	3.9 ± 1.8	4.2 ± 1.8	.253	**4.1 ± 1.8**	**4.8 ± 1.6*****	**.001**
FSH, U/L[a]	5.1 [1.7–16.2]	5.2 [1.9–12.9]	.914	5.1 [1.5–16.7]	5.3 [1.9–15.7]****	.513
Hemoglobin, g/L	149.5 ± 9.8	150.5 ± 9.1	.431	148.5 ± 12.2	149.4 ± 10.1	.594
Total cholesterol, mmol/L	5.7 ± 1.2	5.5 ± 1.0	.278	5.1 ± 1.3****	5.2 ± 1.0*	.345
HDL-cholesterol, mmol/L[a]	1.2 [0.7–2.2]	1.2 [0.7–2.1]	.266	1.1 [0.6–2.1]	1.2 [0.8–1.9]	.062
Triglycerides, mmol/L[a]	**2.0 [0.8–8.5]**	**1.5 [0.6–5.8]**	**.009**	1.6 [0.7–5.1]*	1.5 [0.6–5.8]	.130
LDL-cholesterol, mmol/L	3.4 ± 1.1	3.4 ± 0.9	.607	3.1 ± 1.2**	3.3 ± 1.0	.213
Glucose, mmol/L[a]	5.8 [4.3–9.5]	5.6 [4.1–13.3]	.713	5.7 [4.2–9.4]	5.3 [3.8–9.9]*	.063
HOMA-IR[a]	3.7 [1.1–24.4]	3.1 [0.7–21.8]	.128	**2.3 [0.6–12.5]****	**1.7 [0.5–8.4]****	**.003**
MetS, %	**62.0**	**37.9**	**.000**	56.5*	44.0	.087
Weight, kg	**95.1 ± 16.2**	**90.8 ± 12.8**	**.037**	**95.0 ± 17.6**	**89.6 ± 13.4***	**.015**
BMI, kg/m^2	**31.2 ± 4.5**	**29.5 ± 3.4**	**.002**	**31.5 ± 4.8**	**29.5 ± 3.7**	**.001**
WC, cm	**107.3 ± 10.8**	**103.4 ± 9.6**	**.006**	**109.0 ± 11.6*****	**104.4 ± 10.1***	**.004**
PASE score	197.5 ± 82.0	221.3 ± 96.6	.058	185.2 ± 91.8*	190.2 ± 110.5*	.729
≥1 comorbidity, %	55.3	46.9	.217	71.7****	66.7	.436
Frequent alcohol use, %	24.6	17.7	.220	35.8**	26.5	.171
Current smoker, %	18.3	20.8	.654	13.6	19.6	.241
SF-36 physical function	50.5 ± 7.8	50.3 ± 6.9	.799	**48.3 ± 8.0****	**51.0 ± 8.9**	**.025**
SF-36 mental function	53.1 ± 9.2	52.5 ± 7.2	.580	53.4 ± 8.8	51.7 ± 9.3	.188
BDI	6.6 ± 6.2	5.9 ± 4.7	.332	6.4 ± 6.8	6.4 ± 5.5	.964
PPT rating	24.4 ± 2.4	24.8 ± 2.2	.188	23.7 ± 2.3****	24.0 ± 2.4****	.340
DSST	29.4 ± 8.1	29.9 ± 8.4	.644	28.5 ± 8.0	28.9 ± 8.7	.777

files, with lower high-density lipoprotein (HDL) and higher triglycerides, glucose, and HOMA-IR.

Multiple logistic regression modeling identified obesity (OR = 2.86 [1.67; 4.90]; $P < .0001$) as an independent predictor of isHG (Figure 2A). Substituting WC for BMI categories showed that increased WC was a predictor of isHG (OR = 1.73 [1.07; 2.81], $P = .026$; and OR = 2.64 [1.66; 4.21], $P < .0001$, for WC of 94–102 cm and WC ≥ 102 cm, respectively) and that older men (≥70 y of age) demonstrated a significantly lower predisposition to develop sHG compared to younger subjects (OR = 0.51 [0.28; 0.96]; $P = .035$) (Figure 2C). Weight gain of ≥5% was also a risk factor for isHG (OR = 1.79 [1.15; 2.80]; $P = .011$). No significant interaction effect was found between the variables in the model.

The prevalence of symptoms at baseline and follow-up and new/worsening symptoms during follow-up are shown in Table 2. Men with isHG, compared with pEUG, did not show any difference in the prevalence of symptoms at baseline before or after adjustment (Table 3 and Figure 3A). isHG was associated with a higher prevalence of decreased libido at follow-up, and although just missing statistical significance, the prevalence of erectile dysfunction and infrequent morning erections was higher than pEUG at follow-up (Table 3 and Figure 3B). isHG, however, was significantly associated with the development or worsening of all three sexual symptoms and one physical symptom (impaired vigorous activity) (Table 3). Incremental adjustments for potential confounders (Table 3) showed that isHG maintained its association only with new/worsening sexual symptoms (Figure 3C).

Compared with pEUG, isHG subjects had significantly higher total cholesterol at baseline (Table 4). In addition, isHG was associated with a significant increase in HDL-cholesterol (Table 4). The apparent relationship between isHG with increased HDL-cholesterol became insignificant ($\beta = 0.44$ [−0.08; 0.95]; $P = .096$) after adjusting for those starting lipid-lowering medications during follow-up. isHG men did not differ from pEUG men at baseline, but they showed a significant decrease in the perception of physical well-being (SF-36 physical component score) and deterioration in PPT rating (Table 4).

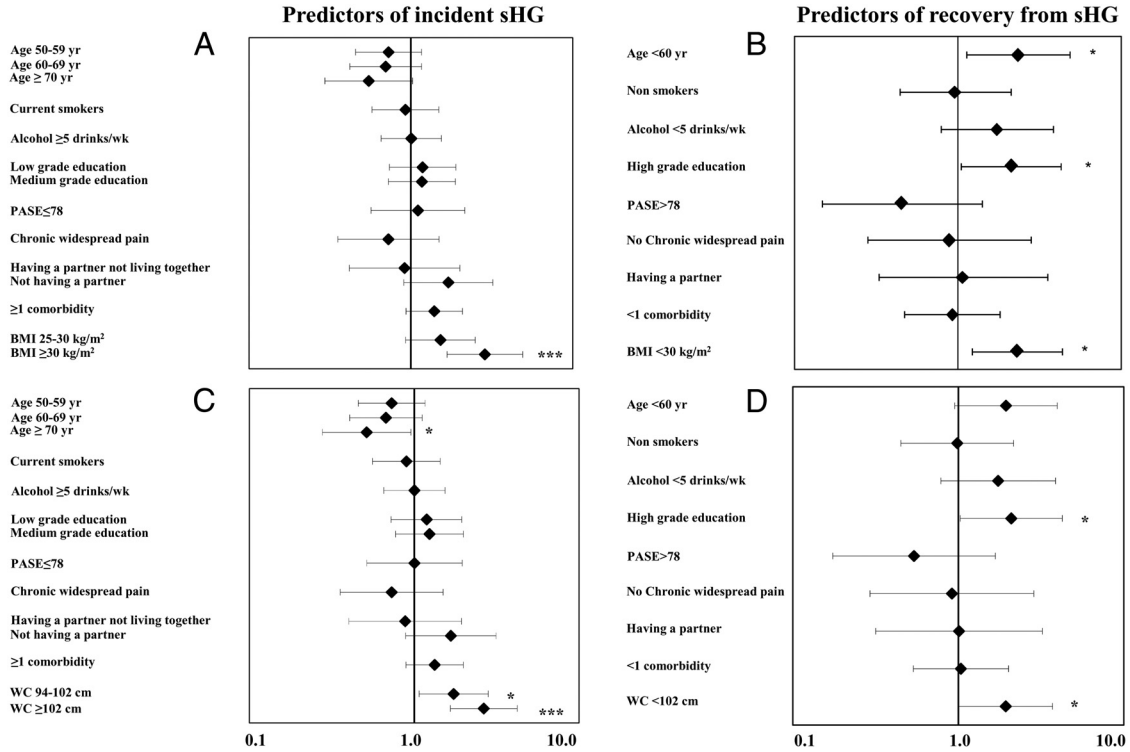

Figure 2. A, Predictors of isHG. Data are derived from multiple binary regression models, using center as a random-effect covariate and age (categorized into 10-y age bands), smoking status (current smoker, yes/no), alcohol intake (alcohol consumption ≥ five per week vs less), education level (low [compulsory education only], medium [noncompulsory education below university level], or high [university education]), PASE score (≤78 and >78), chronic widespread pain (yes/no), marital status (no partner, having a partner not living together, or having a partner and living together), comorbidity (presence/absence of at least one self-reported disorder), and BMI (<25, 25–29.9, and ≥30 kg/m^2) as fixed-effect predictors. Gonadal status was the outcome, with the persistent eugonadal group being the referent category. The ORs are shown on a log scale. B, Predictors of rsHG. Data are derived from multiple binary regression models, using center as a random-effect covariate and age (dichotomized into age < 60 and age ≥ 60 y), smoking status (current smokers, yes/no), alcohol intake (alcohol consumption ≥ five per week vs less), education level (low and medium [completed noncompulsory education but lower than university level] vs high [university education]), PASE score (≤78 and >78), chronic widespread pain (yes/no), marital status (no partner vs having a partner), BMI (<30 and ≥30 kg/m^2), and comorbidity (presence/absence of at least one self-reported disorder) as fixed-effect predictors. Gonadal status was the outcome, with the persistent sHG group being the referent category. The ORs are shown on a log scale. C, Predictors of isHG. Data are derived from multiple binary regression models, using center as a random-effect covariate and age (categorized into 10-y age bands), smoking status (current smoker, yes/no), alcohol intake (alcohol consumption ≥ 5 per week vs less), education level (low [compulsory education only], medium [noncompulsory education below university level], or high [university education]), PASE score (≤78 and >78), chronic widespread pain (yes/no), marital status (no partner, having a partner not living together, or having a partner and living together), comorbidity (presence/absence of at least one self-reported disorder), and WC (<94, 94–102, and ≥102 cm) as fixed-effect predictors. Gonadal status was the outcome, with the persistent eugonadal group being the referent category. The ORs are shown on a log scale. D, Predictors of rsHG. Data are derived from multiple binary regression models, using center as a random-effect covariate and age (dichotomized into age < 60 and age ≥ 60 y), smoking status (current smoker, yes/no), alcohol intake (alcohol consumption ≥ five per week vs less), education level (low and medium [completed noncompulsory education but lower than university level] vs high [university education]), PASE score (≤78 and >78), chronic widespread pain (yes/no), marital status (no partner vs having a partner), WC (<102 and ≥ 102 cm), and comorbidity (presence/absence of at least one self-reported disorder) as fixed-effect predictors. Gonadal status was the outcome, with the persistent sHG group being the referent category. The ORs are shown on a log scale. *, $P < .05$; ***, $P < .0001$.

Characteristics of rsHG

At baseline, rsHG subjects had higher SHBG and total T levels as compared with psHG (Table 1). rsHG men had a more favorable baseline metabolic profile, with lower triglycerides and a lower prevalence of MetS than psHG men. They also showed lower weight, BMI, and WC. rsHG was independently predicted by being younger and having nonobese BMI (OR = 2.32 [1.12; 4.82], $P = .024$; and OR = 2.28 [1.21; 4.31], $P = .011$, respectively) (Figure 2B). Normal WC was a significant predictor for rsHG (OR = 1.93 [1.01; 3.70]; $P = .048$) (Figure 2D). A higher level of education predicted rsHG (OR = 2.11 [1.05; 4.26]; $P = .037$) (Figure 2, B and D). Weight reduction (≥5%) during follow-up, when substituted for BMI, was also a predictor for rsHG (OR = 2.24 [1.04; 4.85]; $P = .042$). No interaction effect was found between the variables in the model.

Prevalences of symptoms at baseline and follow-up as well as recovery/improvement of symptoms during follow-up in psHG and rsHG are shown in Table 2. No significant association was found between rsHG with either baseline or follow-up prevalence or recovery/improve-

Table 2. Symptoms of the Subjects at Baseline and Follow-Up and Data on Incidence/Worsening and Recovery/Improvement

	Baseline			Follow-Up			Incidence/Worsening			Baseline			Follow-Up			Recovery/ Improvement		
Symptoms	**pEUG**	**isHG**	***P***	**pEUG**	**isHG**	***P***	**pEUG**	**isHG**	***P***	**psHG**	**rsHG**	***P***	**psHG**	**rsHG**	***P***	**psHG**	**rsHG**	***P***
Low libido, %	22.7	24.4	.640	**26.2****	**34.4***	**.042**	17.7	25.6	**.029**	22.0	16.0	.266	34.2	29.2*	.448	7.8	6.8	.786
Erectile dysfunction, %	24.8	25.4	.884	30.7****	36.4*	.172	17.3	28.1	**.004**	25.2	20.4	.413	37.9**	28.4	.155	2.8	7.2	.146
Reduced morning erections, %	48.5	48.5	.993	51.3**	58.5	.112	17.7	28.1	**.011**	53.8	55.3	.831	60.0	60.4	.984	8.8	11.1	.577
Reduced vigorous activity, %	19.2	15.1	.236	23.5****	27.3**	.329	13.4	21.4	**.017**	20.7	21.1	.944	25.2	18.0	.214	7.0	9.0	.605
Impairment in walking >1 km, %	4.0	5.1	.550	7.4****	10.6*	.183	5.2	6.5	.547	7.5	3.2	.174	10.2	6.6	.361	1.8	3.4	.459
Impairment in bending, %	4.2	5.1	.641	5.0	6.8	.347	3.7	4.9	.524	5.0	6.3	.666	7.5	3.3	.198	2.6	4.5	.449
Downheartedness, %	3.7	1.5	.176	3.8	3.0	.650	3.4	2.3	.529	5.8	2.1	.184	2.5	3.4	.717	5.1	1.1	.119
Loss of energy, %	3.7	2.9	.621	5.4**	8.1*	.173	4.0	6.0	.264	3.3	1.1	.278	5.9	5.4	.889	1.7	1.1	.713
Fatigue, %	3.7	5.0	.421	4.3	8.1	**.037**	3.2	5.3	.186	4.9	5.3	.908	5.0	2.2	.285	3.4	5.4	.468

P values refer to comparisons between pEUG and isHG subjects or between psHG and rsHG subjects, evaluated by χ^2 test. Asterisks refer to comparison between baseline and follow-up in the same group (pEUG, isHG, psHG or rsHG), evaluated by McNemar's test. *, $P < .05$; **, $P < .01$; ***, $P < .001$; ****, $P < .0001$. Categorical variables were expressed as percentages. Data reported in bold highlight significant differences.

ment of sexual, physical, or psychological symptoms (Figure 3, D–F). rsHG, compared with psHG, had significantly lower total cholesterol and triglycerides at baseline and a significant decrease in insulin during follow-up (Table 4), whereas no significant difference was found for physical and psychological function.

Discussion

The longitudinal data in this observational cohort of older men from the general population highlight the role of obesity and weight gain as the most important predictors for developing sHG, showing for the first time that isHG is associated with appearance or worsening of sexual symptoms only. Another new finding is that sHG is potentially reversible in a substantial proportion of men and that recovery is predicted by nonobesity, weight loss, younger age, and higher education.

Predictors of isHG

As previously shown by cross-sectional data from EMAS, BMI is an important correlate of sHG (*5*). In this longitudinal evaluation, we are able to confirm that higher

Table 3. Prevalence of Symptoms at Baseline, at Follow-Up, and Change During Follow-Up (Incident or Worsened) of HG-Related Symptoms

	Unadjusted	Model 1	Model 2	Model 3	Model 4
Baseline symptoms					
Low libido	1.10 [0.73; 1.66]; *P* = .640	1.22 [0.78; 1.89]; *P* = .390	1.23 [0.79; 1.93]; *P* = .362	1.22 [0.78; 1.91]; *P* = .386	1.47 [0.85; 2.54]; *P* = .171
Erectile dysfunction	1.03 [0.69; 1.54]; *P* = .884	1.14 [0.73; 1.80]; *P* = .564	1.08 [0.68; 1.71]; *P* = .746	1.02 [0.65; 1.63]; *P* = .919	0.96 [0.56; 1.65]; *P* = .891
Reduced morning erections	1.00 [0.71; 1.42]; *P* = .993	1.07 [0.74; 1.55]; *P* = .725	1.00 [0.69; 1.46]; *P* = .976	0.98 [0.67; 1.42]; *P* = .908	1.07 [0.70; 1.64]; *P* = .747
Impairment in vigorous activity	0.75 [0.47; 1.21]; *P* = .237	0.77 [0.47; 1.27]; *P* = .312	0.65 [0.39; 1.08]; *P* = .093	0.61 [0.36; 1.02]; *P* = .058	0.57 [0.31; 1.05]; *P* = .071
Impairment in walking >1 km	1.27 [0.58; 2.82]; *P* = .551	1.38 [0.62; 3.11]; *P* = .432	1.02 [0.43; 2.45]; *P* = .963	0.95 [0.39; 2.30]; *P* = .912	1.06 [0.40; 2.83]; *P* = .903
Impairment in bending	1.21 [0.55; 2.67]; *P* = .642	1.27 [0.57; 2.83]; *P* = .557	1.07 [0.47; 2.40]; *P* = .875	1.05 [0.47; 2.36]; *P* = .913	1.26 [0.52; 3.06]; *P* = .611
Downheartedness	0.39 [0.10; 1.61]; *P* = .192	0.40 [0.10; 1.63]; *P* = .199	0.38 [0.10; 1.56]; *P* = .178	0.35 [0.09; 1.47]; *P* = .153	0.24 [0.03; 1.73]; *P* = .156
Loss of energy	0.77 [0.28; 2.15]; *P* = .622	0.79 [0.28; 2.21]; *P* = .657	0.64 [0.23; 1.80]; *P* = .394	0.58 [0.21; 1.66]; *P* = .311	0.39 [0.09; 1.65]; *P* = .387
Fatigue	1.39 [0.62; 3.07]; *P* = .423	1.42 [0.64; 3.15]; *P* = .394	1.28 [0.56; 2.82]; *P* = .579	1.16 [0.52; 2.63]; *P* = .717	0.93 [0.32; 2.66]; *P* = .889
Follow-up symptoms					
Low libido	**1.47 [1.01; 2.15]; *P* = .043**	**1.79 [1.18; 2.72]; *P* = .007**	**1.75 [1.14; 2.69]; *P* = .010**	**1.73 [1.13; 2.65]; *P* = .012**	**2.22 [1.38; 3.57]; *P* = .001**
Erectile dysfunction	1.30 [0.89; 1.88]; *P* = .173	1.51[0.98; 2.32]; *P* = .060	1.33[0.86; 2.05]; *P* = .200	1.28[0.82; 1.98]; *P* = .277	1.48[0.91; 2.40]; *P* = .117
Reduced morning erections	1.34 [0.93; 1.92]; *P* = .113	**1.48 [1.01; 2.18]; *P* = .044**	1.34 [0.91; 1.98]; *P* = .140	1.32 [0.89; 1.95]; *P* = .164	1.40 [0.90; 2.26]; *P* = .138
Impairment in vigorous activity	1.22 [0.82; 1.81]; *P* = .330	1.36 [0.89; 2.09]; *P* = .156	1.16 [0.75; 1.80]; *P* = .506	1.10 [0.71; 1.71]; *P* = .673	1.02 [0.61; 1.70]; *P* = .949
Impairment in walking >1 km	1.48 [0.83; 2.65]; *P* = .186	1.73 [0.93; 3.22]; *P* = .081	1.35 [0.71; 2.57]; *P* = .362	1.27 [0.66; 2.43]; *P* = .473	1.17 [0.54; 2.54]; *P* = .697
Impairment in bending	1.40 [0.69; 2.85]; *P* = .349	1.53 [0.74; 3.16]; *P* = .251	1.11 [0.51; 2.41]; *P* = .797	1.05 [0.48; 2.30]; *P* = .899	1.07 [0.44; 2.62]; *P* = .884
Downheartedness	0.79 [0.28; 2.20]; *P* = .651	0.81 [0.29; 2.26]; *P* = .685	0.57 [0.17; 1.84]; *P* = .343	0.53 [0.16; 1.73]; *P* = .295	0.51 [0.12; 2.14]; *P* = .505
Loss of energy	1.57 [0.82; 3.00]; *P* = .176	1.64 [0.85; 3.15]; *P* = .139	1.37 [0.71; 2.67]; *P* = .353	1.30 [0.67; 2.54]; *P* = .439	1.10 [0.48; 2.52]; *P* = .819
Fatigue	**1.98 [1.03; 3.83]; *P* = .041**	**2.05 [1.06; .97]; *P* = .034**	1.81 [0.92; 3.55]; *P* = .084	1.70 [0.86; 3.34]; *P* = .126	1.66 [0.76; 3.67]; *P* = .207
Incident/worsening symptoms					
Low libido	**1.60 [1.05; 2.46]; *P* = .030**	**1.79 [1.13; 2.83]; *P* = .013**	**1.77 [1.11; 2.82]; *P* = .017**	**1.74 [1.09; 2.78]; *P* = .021**	**2.16 [1.29; 3.62]; *P* = .003**
Erectile dysfunction	**1.86 [1.21; 2.86]; *P* = .005**	**2.09 [1.31; 3.32]; *P* = .002**	**1.91 [1.19; 3.06]; *P* = .007**	**1.87 [1.16; 3.00]; *P* = .010**	**2.12 [1.27; 3.56]; *P* = .004**
Reduced morning erections	**1.82 [1.14; 2.91]; *P* = .012**	**1.98 [1.21; 3.23]; *P* = .006**	**1.90 [1.15; 3.13]; *P* = .012**	**1.88 [1.14; 3.09]; *P* = .014**	**1.79 [1.02; 3.16]; *P* = .044**
Impairment in vigorous activity	**1.77 [1.10; 2.85]; *P* = .019**	**1.91 [1.16; 3.16]; *P* = .011**	**1.75 [1.06; 1.09]; *P* = .030**	**1.66 [1.00; 2.75]; *P* = .050**	1.42 [0.78; 2.60]; *P* = .255
Impairment in walking >1 km	1.26 [0.60; 2.65]; *P* = .548	1.43 [0.66; 3.12]; *P* = .368	1.23 [0.56; 2.68]; *P* = .610	1.46 [0.52; 2.52]; *P* = .735	1.12 [0.45; 2.83]; *P* = .806
Impairment in bending	1.32 [0.56; 3.11]; *P* = .526	1.44 [0.60; 3.46]; *P* = .410	0.98 [0.38; 2.56]; *P* = .973	0.91 [0.35; 2.38]; *P* = .848	0.80 [0.24; 2.71]; *P* = .721
Downheartedness	0.69 [0.21; 2.22]; *P* = .531	0.70 [0.22; 2.28]; *P* = .557	0.68 [0.21; 2.21]; *P* = .518	0.65 [0.20; 2.11]; *P* = .468	0.62 [0.15; 2.64]; *P* = .521
Loss of energy	1.53 [0.72; 3.25]; *P* = .268	1.57 [0.74; 3.34]; *P* = .241	1.36 [0.63; 2.92]; *P* = .429	1.32 [0.61; 2.84]; *P* = .478	1.09 [0.42; 2.81]; *P* = .867
Fatigue	1.71 [0.77; 3.83]; *P* = .191	1.76 [0.78; 3.95]; *P* = .172	1.62 [0.72; 3.68]; *P* = .247	1.54 [0.68; 3.52]; *P* = .302	1.49 [0.57; 3.91]; *P* = .418

Data are expressed as OR [95% CI] of logistic regression analysis comparing incident sHG with EUG men (referent). Model 1 is adjusted for age and center; model 2 is adjusted for age, center, and BMI; model 3 is adjusted for age, center, BMI, and presence of comorbidities; and model 4 is adjusted for age, center, BMI, presence of comorbidities, and drinking and smoking habits. Data reported in bold highlight significant differences.

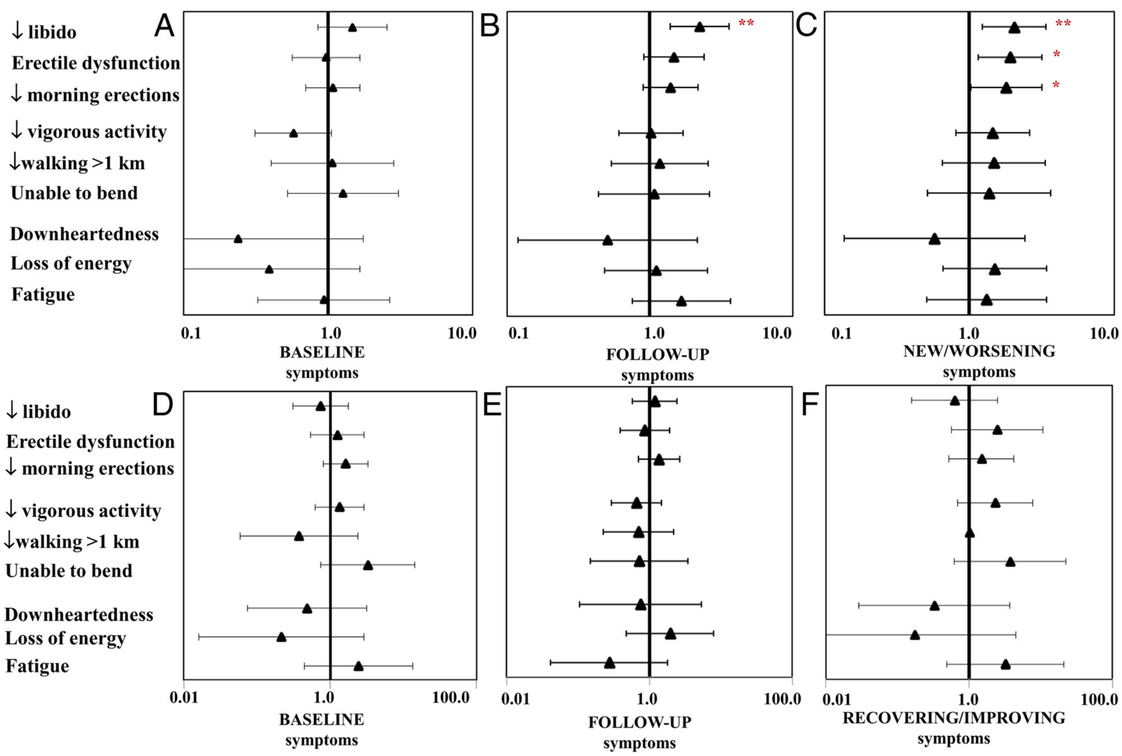

Figure 3. Upper panels, Association between incidence of sHG and baseline prevalence (A) or follow-up prevalence (B) or incident/worsening (C) of hypogonadism-related symptoms (adjusted for age, center, BMI, comorbidities, smoking habits, and alcohol intake), using the group of persistent eugonadal subjects as referent category. The ORs are shown on a log scale. Lower panels, Association between recovery from sHG and baseline (D) or follow-up (E) prevalence or recovery/improvement (F) of hypogonadism-related symptoms (adjusted for age, center, BMI, comorbidities, smoking habits, and alcohol intake), using the group of persistent sHG subjects as referent category. The ORs are shown on a log scale. *, $P < .05$; **, $P < .01$

BMI and WC predict isHG. Our finding of obesity as a determinant for T decline, independent of LH, confirms earlier longitudinal results (16, 17). The association between obesity and hypogonadism is complex and poorly understood. Obesity can induce peripheral and central insulin resistance (18), proinflammatory cytokine production (TNFα and IL-6) from adipocytes (19), and central nervous system endocannabinoid release (20) that can induce down-regulation of hypothalamic function. In addition, adipocytokines such as leptin and adiponectin have

Table 4. Association between isHG or rsHG and Baseline or Percentage Change From Baseline of Hematological and Metabolic Parameters and Test Scores Evaluating Physical or Psychological Health

	isHG				rsHG			
	Baseline		% Change From Baseline		Baseline		% Change From Baseline	
	β Coefficient [95%CI]	P	β Coefficient [95%CI]	P	β Coefficient [95%CI]	P	β Coefficient [95%CI]	P
Hematological and metabolic parameters								
Hemoglobin, g/L	−1.99 [−4.1; 0.09]	.060	−1.30 [−2.78; 0.17]	.083	1.95 [−0.86; 4.76]	.173	0.17 [−1.71; 2.04]	.861
Total cholesterol, mmol/L	**0.21** [**0.01; 0.41**]	**.040**	−2.39 [−5.77; 0.99]	.166	**−0.33 [−0.64; −0.02]**	**.038**	4.37 [−0.70; 9.44]	.090
HDL-cholesterol, mmol/L[a]	−0.01 [−0.05; 0.04]	.689	**0.50** [**0.01; 0.98**]	**.044**	−0.01 [−0.09; 0.07]	.729	−0.22 [−0.74; 0.29]	.388
Triglycerides, mmol/L[a]	0.06 [−0.05; 0.16]	.275	0.22 [−0.17; 0.60]	.267	**−0.18** [**−0.35; −0.01**]	**.041**	0.29 [−0.44; 1.01]	.433
LDL-cholesterol, mmol/L	0.16 [−0.02; 0.34]	.084	−3.06 [−8.58; 2.46]	.277	−0.19 [−0.49; 0.11]	.210	5.30 [−3.64; 14.23]	.243
Glucose, mmol/L[a]	0.01 [−0.02; 0.04]	.485	0.30 [−0.02; 0.63]	.066	0.03 [−0.04; 0.10]	.350	−0.06 [−0.59; 0.46]	.814
Insulin, mU/L[a]	0.09 [−0.02; 0.19]	.114	0.20 [−0.31; 0.70]	.442	0.05 [−0.12; 0.23]	.545	**−1.16** [**−2.20; −0.13**]	**.029**
HOMA-IR[a]	0.10 [−0.02; 0.21]	.114	−0.12 [−0.63; 0.39]	.654	0.08 [−0.12; 0.29]	.412	−0.88 [−2.02; 0.26]	.125
Tests scores for physical or psychological health								
SF-36 physical function	1.19 [−0.21; 2.58]	.095	**−3.61** [**−6.85; −0.365**]	**.029**	−0.64 [−2.94; 1.66]	.581	4.40 [−0.69; 9.49]	.089
SF-36 mental function	1.44 [−0.28; 3.16]	.102	−6.81 [−32.94; 19.32]	.609	1.09 [−1.45; 3.64]	.397	−7.50 [−15.40; 0.48]	.085
BDI	−0.01 [−1.17; 1.16]	.994	11.55 [−17.11; 40.21]	.429	−1.16 [−2.91; 0.59]	.191	47.06 [−0.10; 93.52]	.100
PPT rating	0.24 [−0.21; 0.70]	.298	**−2.65** [**−4.57; −0.74**]	**.007**	0.29 [−0.37; 0.95]	.384	−1.12 [−3.87; 1.63]	.423
DSST	0.53 [−0.92; 1.98]	.477	−3.43 [−7.35; −0.49]	.086	−0.04 [−2.36; 2.29]	.976	−0.65 [−8.94; 7.64]	.877

Abbreviation: LDL, low-density lipoprotein. Data are adjusted for age, center, BMI, presence of comorbidities, drinking, and smoking habits. The group of eugonadal subjects at baseline was used as the referent category for the group of isHG, whereas the group with psHG was used as the referent category for the group that recovers from sHG. Data reported in bold highlight significant differences.

[a] Paired and unpaired *t* tests have been performed using natural log-transformed data for normalizing skewed distributed variables.

been shown to modulate GnRH and gonadotropin secretion (21) and to influence testicular T production (22). Conversely, the suggested role for an excess of estrogens, due to an increased aromatase activity in obese subjects, in reducing the GnRH-gonadotropin secretion has not been confirmed in obese diabetic (23) and nondiabetic men (5), their estradiol levels being lower, rather than higher, and correlated with T levels but not with BMI.

Our results also demonstrated a lower probability that older men will develop sHG. Cross-sectional data from EMAS have shown that aging is associated with elevated gonadotropins and primary hypogonadism (1, 5). Disorders causing a derangement of hypothalamic-pituitary axis superimposed on a background of high gonadotropin (as in older men) are less likely to suppress LH to values below the threshold used to define sHG. Men who attended both phases of the study are healthier as compared with those who did not (Supplemental Table 1). It is therefore conceivable that among those attending for follow-up, a survival bias may have selected healthier older men who are less prone to develop sHG (24).

Developing sHG: clinical features

In this study, development of sHG was associated, independently of BMI, comorbidities, and lifestyle, with new or worsening sexual symptoms but not physical or psychological ones. This is consistent with our previous cross-sectional analyses (8) indicating that these three sexual symptoms are the most specific subjective features associated with low T. In addition, to confirm the substantial baseline prevalence (22.7–48.5%) of sexual symptoms, occurrence of new or worsening symptoms in the pEUG men is not negligible (almost 18%), albeit at a lower rate than in isHG men (25.6–28.1%), thus accounting for the weaker association between isHG and increased prevalence of sexual symptoms at follow-up. This emphasizes the importance of the co-occurrence of all three sexual symptoms for increasing the probability of a robust syndromic clustering with low T (8), which serves to provide the operational definition of symptomatic hypogonadism or late-onset hypogonadism. The longitudinal results, showing a specific association between the development of sHG with the appearance or worsening of all three sexual symptoms prospectively, strongly endorse this approach.

In the cross-sectional analyses, physical or psychological symptoms did not cluster together with low T, but one of the physical symptoms, decreased vigor, did show an inverse correlation with T levels (8). Interestingly, in the longitudinal study, decreased vigorous activity is the only nonsexual symptom whose new occurrence or worsening was significantly associated with isHG, until smoking and alcohol habits were included as covariates. This emphasizes the nonspecific nature of nonsexual symptoms in sHG. However, when considering the objective evaluation of physical performance (PPT rating), a significantly greater reduction was found in isHG men, although this was not translated into a subjective perception of deterioration.

Predictors of rsHG

The present results show that sHG is frequently reversible (42.9% when excluding or 30.2% when not excluding the subjects not attending the second assessment). Reversion to EUG was predicted by lower BMI and WC, weight loss, younger age, and higher education. The weight associations are compatible with recent evidence from a general population showing that weight loss is associated with a proportionate increase in T levels (4, 25). Thus, a >5% weight loss was associated with a significant increase of T levels with the maximum effect in those men who lost ≥15% of weight when LH as well T increased contemporaneously (4). Supervised dieting/exercise or bariatric surgery in obese men has been shown to increase T and LH levels proportionally to the amount of weight loss (26). Interestingly, T increase attained in treated subjects was higher in younger individuals (26). We found, in addition to lower weight, that younger age was an independent predictor of rsHG, suggesting that the potential for weight loss to improve hypothalamic-pituitary function may be eroded by adverse effects of aging. A novel finding is that a higher level of education was an independent predictor of rsHG. Education is a socioeconomic status surrogate and an important determinant of health inequality. Higher education is a protective factor for cardiovascular diseases and all-cause mortality (27, 28). Changes in behavior in response to health education are most beneficial in higher socioeconomic groups (27–29), which may translate into improved metabolic status and avoidance of obesity. Taken together, these results strongly suggest that sHG or functional hypothalamic suppression associated with obesity is potentially reversible with weight loss and amenable to lifestyle-influenced metabolic modifications especially in younger educated men. Weight loss, especially in older men, can be unintentional and due to comorbidities, cancer cachexia, or other wasting diseases. However, excluding men with incident cancer or heart diseases in our analyses did not influence the relationships between BMI or weight loss with rsHG (data not shown), suggesting that the observed weight loss in those obese middle-aged men (mean age, 56 y) with rsHG may well have been intentional and that the concomitant rise in T is part of the overall, positive health outcome.

Recovering from sHG: clinical features

In this study, the anticipated association between rsHG and resolution/improvement of symptoms was not found. There are a number of possible explanations. The relatively small sample size may not provide sufficient statistical power to detect small differences between psHG (n = 123) and rsHG (n = 96), with a minority (two to 11 men) only showing symptomatic improvements. Both groups are subjected to uncontrolled multiple and multidirectional influences during follow-up in this noninterventional observational study. The increase in T documented at one time point at follow-up may not represent a sufficiently sustained improvement to transmute into subjective symptomatic recovery. Randomized controlled trials of T replacement therapy demonstrating improvements in sexual function (30), physical strength (31), and depressive symptoms (32) usually show a 2-fold increase of T levels into the mid-normal physiological range during treatment, for a minimum of 24 weeks. The spontaneous rise in T levels observed in our rsHG subjects is relatively small by comparison (9.2 nmol/L at baseline, increasing to 13.3 nmol/L at follow-up or a 45% increment) and may not be sufficient to drive improvements or resolution of sexual symptoms. Given the high prevalence of sexual symptoms irrespective of the concentration of circulating T, a further explanation could be that important nonhormonal (eg, psychosocial and relational) factors contribute to the persistence of symptoms, even after restoration of normal T levels.

Strengths and limitations

The strengths of this study include a large unbiased sample from the general population, the prospective design providing noninterventional longitudinal data to investigate the natural history and predictors of hypogonadism, and the standardized instruments applied across centers and between the phases of the study. T levels were measured by liquid chromatography–tandem mass spectrometry, with paired baseline and follow-up samples analyzed simultaneously. Limitations in EMAS have been described previously (13). The study interval of 4.3 years may be relatively short for capturing the more subtle changes in signs and symptoms of hypogonadism in an observational study. A single LH measurement only was available to categorize hypogonadism, but its collinearity with FSH would have minimized any potential misclassification. Also for T, a single measurement only was available at each time point. However, T is a stable analyte (33), and single measurements of T on morning samples can provide representative and reliable data in large epidemiological studies such as the EMAS.

Conclusions

Our longitudinal data showed that obesity or weight gain predisposed older men to develop sHG. Older men were at lower risk. Development of sHG was associated with the appearance of new or worsening sexual, but not physical and psychological, symptoms. sHG frequently remits; this is predicted by lower BMI, lower WC, or weight loss, as well as younger age and higher education. Biochemical reversal of sHG to EUG, however, was not accompanied by a significant symptomatic improvement. Further studies are indicated to corroborate and extend the present results.

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