Published in final edited form as:

J Am Geriatr Soc. 2008 May ; 56(5): 831–839. doi:10.1111/j.1532-5415.2008.01679.x.

The Natural History of Symptomatic Androgen Deficiency in Men: Onset, Progression, and Spontaneous Remission

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Abstract

OBJECTIVES—To describe the onset, progression, and remission of symptomatic androgen deficiency (SAD) using longitudinal data from the Massachusetts Male Aging Study (MMAS).

DESIGN—A prospective, population-based study of men living in Boston, Massachusetts. Data were collected in three waves: T1 (1987/89), T2 (1995/97), T3 (2002/04). Onset, progression, and remission were defined in terms of transitions in SAD status from one wave to the next.

SETTING—In-person, in-home interviews.

PARTICIPANTS—Seven hundred sixty-six community-dwelling men aged 40 to 70 at baseline (T1) contributed data from T1 to T2 and 391 from T2 to T3.

MEASUREMENTS—SAD was defined in terms of serum total and free testosterone (T) levels and symptoms associated with low circulating androgens. Total T and sex hormone-binding globulin (SHBG) were measured using radioimmunoassay. Free T was calculated from total T and SHBG measurements.

RESULTS—At T2 or T3, the likelihood of SAD was markedly greater for subjects who had exhibited SAD at the previous wave (odds ratio = 3.8, 95% confidence interval = 1.9–7.4), overall 55% of subjects who exhibited SAD experienced remission by the next study wave. The probability of SAD was greater with older age and greater body mass index. Multivariate models demonstrated that the likelihood of remission was at least 50% for most subpopulations.

CONCLUSION—Over approximately 15 years of follow-up, SAD did not represent a stable health state. The likelihood of SAD would remit exceeded the likelihood that it

Keywords

aging; men; androgen; population study

Gradual decreases in serum testosterone (T) concentrations are generally believed to accompany male aging.^{1–8} Low T levels have been shown to contribute to diabetes mellitus,

low bone and muscle mass, impaired sexual function, and frailty,^{9–13} so interventions intended to slow or reverse age-related declines in T have attracted a great deal of attention. Whether there exists a threshold at which T levels should be considered “deficient” is still the subject of substantial debate.^{14–16} Although it is known that comorbidity and health behaviors influence T,^{8,17} concurrent changes in health do not appear to account for age-related declines in T.^{8,18} In addition, T levels exhibit substantial random variability over periods of weeks or months.^{19,20} The presence or absence of true age-related hypogonadism is therefore difficult to determine.²¹

For these reasons, it has been proposed that a composite measure of T levels and seemingly related symptoms, many of them having to do with mood and self-assessed well-being, may represent a more clinically meaningful assessment of male hormonal status.^{22–28} Implicit in this claim is the idea that such a composite, which we refer to as apparent symptomatic androgen deficiency (SAD), should represent a more temporally stable description of androgen status than measurements of T alone. No longitudinal analyses have yet been performed to support this contention, and the lack of consistent associations between T and ostensibly related symptoms may call it into question.²⁹

To address this issue, data from 762 men enrolled in the longitudinal Massachusetts Male Aging Study (MMAS), a population-based study of men aged 40 to 70 at baseline, with three data collection waves between 1987 and 2004, were examined. The overarching goal of the analysis was to establish the proportion of men whose SAD status changed between study visits. It was hypothesized that, over time, a substantial proportion of men would exhibit SAD who had not previously done so (would experience SAD onset). It was further hypothesized that, consistent with the notion that SAD is stable or reliable, subjects who exhibited SAD would continue to do so (that few subjects would experience remission) and that the likelihood of SAD onset or remission would vary substantially as a function of age and body mass index (BMI). Finally, it was speculated that the age-specific probability of SAD would increase as a function of calendar time, consistent with previous observations of substantial secular decreases in serum T levels.³⁰

METHODS

Study Design and Data Collection

The institutional review board of the New England Research Institutes (NERI) approved all activities. The MMAS design is described in detail elsewhere.^{2,31,32} Briefly, a random sample of male residents of greater Boston, Massachusetts, was obtained from U.S. census reports. There were three data collection waves: T1 (1987/89), T2 (1995/97), and T3 (2002/04). During the baseline period (T1), trained interviewers and phlebotomists visited 1,709 subjects in their homes. Each subject provided information concerning his health and life circumstances, along with a nonfasting blood sample. Follow-up data were obtained on 1,156 subjects at T2 and 853 subjects at T3.

Elements of study design may influence serum hormones.³³ The MMAS therefore took steps to minimize bias and imprecision. Blood samples were drawn within 4 hours of subjects' waking to reduce the effect of diurnal variation in hormone concentrations.³⁴ To

counteract episodic hormone secretion,³⁵ two samples were obtained at each visit, 30 minutes apart, and were pooled in equal aliquots at the time of assay. Blood was centrifuged within 6 hours of study visit. Serum was stored in 5-mL scintillation vials at -20°C , shipped to the laboratory within 1 week by same-day courier, and stored at -70°C until the time of assay. All assays were performed at the Endocrine Laboratory, University of Massachusetts Medical Center, under the direction of Christopher Longcope, MD. Stored T1 samples were assayed for total T in 1994, and T2 and T3 samples were assayed shortly after blood collection. A 2000 analysis of stored T1 and T2 samples revealed no evidence of storage artifact or assay drift.²⁸

Total T was measured using radioimmunoassay kits from Diagnostic Products Corporation (Los Angeles, CA). Interassay coefficients of variation (CVs) were 8.0%, 9.0%, and 8.3% at T1, T2, and T3, respectively. Sex hormone-binding globulin (SHBG) was measured using radioimmunoassay kits at T1 and T2, and at T3 with chemiluminescent enzyme immunometric assay using the Diagnostic Products Corporation Immulite technology; interassay CVs were 10.9%, 7.9%, and 3.0% at T1, T2, T3, respectively. Free T was calculated using mass action equations described previously,³⁶ with association constants taken from another previous study.³⁷

Demographic characteristics, employment status, history of physician-diagnosed chronic illness, self-assessed health, smoking status, and daily alcohol consumption³⁸ were obtained from self-report. Height and weight were measured using methods developed for use in large-scale epidemiological field work.³⁹ Medication usage was obtained using a comprehensive physical inventory of medication containers.

Definition of SAD

The operational definition of SAD employed in the MMAS has been previously described.²⁸ To maintain consistency with prior results,^{28,40,41} definitions previously employed were used. Up to eight potential symptoms (Table 1), in combination with early-morning nonfasting measurement of T, indicated SAD; symptoms were initially chosen so as to adhere to contemporary guidelines as closely as possible. Five of the potential symptoms were items excerpted from the 20-item Center for Epidemiological Studies-Depression Scale (CES-D)⁴² questionnaire; these were rated on a 4-point ordinal scale. (Subjects indicated that they experienced the symptom rarely or none of the time, some or a little of the time, occasionally or a moderate amount of the time, or most or all of the time.) For these, a specific symptom was considered present if any of the latter three categories was chosen. The presence of minimal, moderate, or complete erectile dysfunction (ED) indicated ED. MMAS T1 measurements predated the use of a validated single-item assessment⁴³ of ED, so baseline ED categories were themselves constructed from a composite of 13 items detailing self-reported erectile functioning.⁴¹ ED was measured using a single question at T2 and T3. Subjects' statements that they did not experience sexual feelings or thoughts more often than once per month indicated low libido.⁴⁰ Finally, depression was defined as current use of any antidepressant medication as part of a full medication inventory.

In the composite measure, the presence of at least three of the eight symptoms in combination with (1) serum total T levels less than 200 ng/dL or (2) total serum T of 200 to

400 ng/dL and free T less than 8.91 ng/dL indicated apparent SAD. These requirements are less restrictive than the more recently published Clinical Practice Guideline (CPG) for diagnosis of androgen deficiency as recommended by the Endocrine Society,²² a closer approximation of which was also considered in secondary analyses described below.

SAD onset was defined as a subject meeting the definition of SAD who had not at the previous study wave. Remission was defined as a subject not meeting this definition who had done so at the previous study wave. SAD progression was defined as an increase in the number of symptoms of SAD over time or a decrease in serum T concentrations, given a history of SAD. Because each of these definitions requires knowledge of previous SAD status, they were defined at T2 and T3 only, where these were modeled as a function of T1 and T2 data, respectively.

Analytic Sample

Data were included on all MMAS subjects for whom T and SHBG measurements were available. Exclusion criteria included outlying total T concentrations (>1,200 ng/dL), use of medications that might influence serum hormone concentrations (determined by an independent endocrinologist as previously reported¹⁸), or diagnosis of prostate cancer, for which hormone suppression therapy could not be excluded as a possible external source of reductions in androgen concentrations. Because the focus of the analysis was on SAD transitions (onset or remission), a subject was entered into the analysis only if he contributed data up to at least T2.

A total of 1,517 subjects were eligible for inclusion at study baseline (T1). Of these, 884 had T and SHBG concentrations at T2 and no prior diagnosis of prostate cancer, although 122 of these 884 reported the use of hormonally active medications at T2 (including 4 who were using T replacement therapy), leaving 762 men available for analyses of SAD transitions between T1 and T2. Of these, 465 had complete hormone data and no diagnosis of prostate cancer at T3, but an additional 74 were removed from the T3 analysis subset because of prescription medications that might affect hormone levels, leaving a total of 391 records available at T3. The final data set therefore consisted of 1,153 from 762 subjects.

Statistical Analysis

Exploratory graphical analyses employed Generalized Additive Models⁴⁴ for scatterplot smoothing followed by formal inference and estimation using a logistic regression model. Outcomes were modeled taking account of subjects' SAD status and covariate data at the previous study wave.

Construction of Regression Models—The initial, “base” model considered SAD status as a function of a subject's age, his previous SAD status, the time in years since his last study visit, and an indicator of study wave; the last variable would allow for any secular trend in the prevalence of SAD, presumably corresponding to that previously observed in T values.³⁰ Subsequent models included additional covariates. Time in years since previous study visit was included to accommodate intersubject variation in lag times and also in recognition of the fact that the lag times between T1 and T2 (7.1–10.4 years, median 8.9

years) were greater than those between T2 and T3 (5.9–7.6 years, median 6.3 years). This variable was centered at 7.5 years, which falls inside both of those ranges. The statistical significance of individual regression estimates was determined using Wald-type test statistics. All covariates displaying significant association (at the .05 level) with SAD status, controlling for the base model covariates, were then entered into a larger, “full” model. From this, a reduced, “final” model was obtained using backwards stepwise elimination of nonsignificant effects based on Wald statistics and consideration of overall model fit, as quantified by the Akaike Information Criterion.⁴⁵

Estimation—Each subject could contribute up to two records (transitions). Therefore, models were fit using random-effects logistic regression, with subject-specific intercepts to account for intrasubject correlation in outcome measurements. Estimation used maximum likelihood with numerical integration using Gaussian quadrature.⁴⁶ Because computational tools to fit these models are new and can sometimes behave erratically, all models were replicated in two different software packages. The xtlogit procedure in Stata, version 9.0 (StataCorp, College Station, TX) and the glmmML library⁴⁷ in R version 2.5.0 (The R Foundation for Statistical Computing, Vienna, Austria) were used, and equivalent results were obtained.

RESULTS

Seven hundred sixty-two subjects contributed at least one study wave transition; of these, 391 contributed two. Descriptive data are displayed in Tables 2 and 3. Because approximately 9 years elapsed between T1 and T2, the age distribution extends to 80 years for the second transition (to predict outcomes at T3).

Between T1 and T2, there was an increase in the prevalence of hypertension and in the number of medications used and a sharp decrease in the prevalence of smoking, whereas self-assessed health exhibited mild improvement with time. Average total T exhibited a gradual decrease over the course of the study as subjects aged. Decreases in free T outstripped these decreases, as is consistent with previously reported results.^{2,8} Of the eight symptoms and signs of SAD, loss of libido, erectile dysfunction, and sleep disturbance exhibited the greatest increases in prevalence. The components of SAD did not vary substantially according to the number of records donated by study subjects. For instance, in all subjects considered, mean total T at T2 was 455 ng/dL, whereas in the 391 subjects who contributed two transitions, mean total T at T2 was 456 ng/dL.

Exploratory Models

Crude SAD Status—Figure 1 details SAD status of subjects eligible for onset or remission. At T2 or T3, the unadjusted likelihood of SAD in subjects who had SAD at the previous wave was three to four times as high as that in subjects who did not. For instance, 12 (31%) of 39 eligible subjects who had SAD at T1 continued to exhibit SAD at T2, whereas only 69 (10%) of eligible subjects exhibited onset of SAD between T1 and T2.

From T2 to T3, approximately 17% of eligible subjects experienced SAD onset, although the crude rate of onset between T2 and T3 was nearly identical for subjects who exhibited

SAD at T1 and those that did not, indicating that the assumption that T2 status mediated associations between T1 and T3 (see Methods) is reasonable. Overall, there were 1,083 potential instances of SAD onset. Of these, 129 (12%) resulted in an instance of SAD onset (69 subjects exhibited SAD onset from T1 to T2 and an additional 60 from T2 to T3; Figure 1).

The proportion of eligible subjects who exhibited remission of SAD was strikingly high. Of 70 subjects who were eligible for remission and were observed in follow-up, 39 (55%) did not exhibit SAD at the relevant follow-up wave.

The majority of subjects classified as exhibiting SAD had total T values not in the very low range but between 200 and 400 ng/dL. For instance, of the 81 subjects classified with SAD at T2, only 10 (12%) had total T < 200 ng/dL.

Association Between SAD and Age and BMI—In previous analyses, age and BMI were strongly associated with within-subject changes in serum T concentrations.^{8,48,49} Both were also powerful predictors of transitions in SAD status. Figure 2 provides a depiction of onset and remission between T1 and T2 generated from fitting a Generalized Additive Model.⁴⁴ In models controlling for base covariates (age, time since baseline study visit, study wave, and previous SAD status), there was a strong association between BMI and the likelihood of SAD. For instance, for a hypothetical 55-year-old man with SAD, the model-estimated probability of remission 7.5 years later would be approximately 75% if his BMI was 25 kg/m², versus 48% if his BMI was 35 kg/m².

Overall, exploratory model-based estimates were consistent with crude computations. For instance, it was observed that 32 (8%) of 400 eligible subjects younger than 60 experienced SAD onset at T2 or T3. SAD onset was 2.5 times as likely in eligible subjects aged 70 and older; 55 of 281 (20%) of eligible subjects aged 70 and older experienced SAD onset. These estimates were consistent with the smoothed trends depicted in Figure 2.

Multivariate Logistic Regression Results

Base Model—Logistic regression models were used to quantify the likelihood of AD progression or remission as a function of covariates treated simultaneously. The left-hand column of Table 4 gives preliminary regression estimates for the base model—depicted above the horizontal line dividing the table—as well as the effects of additional covariates added to the base model individually. In the base model, age and previous SAD status were strongly associated with SAD. A decade of age, for instance, was associated with an odds ratio (OR) of 1.7, indicating a 70% increase in the odds of SAD per 10 years of age, controlling for previous SAD status, study wave, and years since previous interview. This translates to a 70% increase per decade in the odds of SAD onset (which assumes no SAD at the previous study wave) and an approximate 40% decrease per decade in the odds of SAD remission. These estimates are consistent with those obtained in exploratory models as depicted in Figure 2, in which the estimated probability of remission was .79 for subjects 50 years old (yielding odds of approximately 3.8 to 1 in favor of remission) and .71 for subjects 60 years old (yielding odds of approximately 2.5 to 1), translating to an approximate 36% decrease in the odds of remission between the ages of 50 and 60.

When adjusted for the components included in the base model, BMI and general health status—the latter measured according to medication usage, physician diagnosis of comorbidity (diabetes mellitus or hypertension), or a subjects' statement that his health was less than excellent—were significantly associated with SAD status when base model covariates were considered. Other effects exhibited no meaningful associations with SAD and were discarded.

Expanded Models—The middle and right-hand columns of Table 4 document the full model (including all effects that were significant when considered only in the context of the base model) and the final model (see above). In the full model, the size and statistical significance of effects was somewhat less than the base model effects, particularly with regard to comorbidities, medication usage, and overall health status, which is to be expected, given their considerable interrelatedness. Stepwise removal of these effects indicated that, of these three components, the individual comorbidities contributed least to model fit. As measured according to Akaike Information Criterion, a model including medication usage and self-reported health was most efficient and is depicted as the final model in the right-hand column of Table 4. Results indicate that, controlling for other factors, subjects in excellent general health or who were taking no medications were at lower risk of SAD than others, although no dose-response relationship was found between number of medications (or decreasing health status) and odds of SAD once age and previous SAD status were taken into consideration. Most notably, age and BMI remained strongly associated with the risk of SAD, as did SAD at the previous study wave, which obtained a final OR of 3.8 (95% confidence interval (CI) = 1.9–7.4).

Unlike in models of T levels themselves,³⁰ no secular trends were observed in the likelihood of SAD once age, health, and body composition had been taken into account, as indicated by the decrease in the regression effect associated with study wave from 1.4 in the base model to 1.0 in the final model.

The Pattern of Remission—Both increases in T levels and decreases in the number of symptoms appeared to contribute to the high rate of remission of SAD. For instance, of the 27 subjects who exhibited remission of SAD between T1 and T2, total T levels increase to more than 400 ng/dL in 16, and an additional three exhibited free T above 8.91 ng/dL, so that approximately two-thirds of remission could be attributed to increases in T levels, whereas the remaining one third was attributable to decreases in the prevalence of symptoms alone.

Lack of Progression of AD—Little evidence was found to suggest the worsening of SAD with time. When all subjects were considered, the number of SAD symptoms increased with time even as T levels declined, although this was not the case in subjects who exhibited SAD. For those men, the mean number of symptoms decreased by 0.6 symptoms (95% CI = 0.2–0.9) from one visit to the next, whereas total and free T increased by 62 ng/dL (95% CI = 29–94) and 1.0 ng/dL (95% CI = 0.1–1.9), respectively, as was consistent with the overall trend toward remission of SAD once it was observed.

Comparison with Results Using CPG

The Endocrine Society's most recent CPG²² distinguishes between two sets of symptoms ostensibly related to low circulating androgens. Of those included in the CPG, the MMAS collected data on two "suggestive" symptoms (reduced libido and erectile dysfunction) and five "associated" symptoms (lethargy, sleep disturbance, depressed mood, loss of concentration, and irritability), as defined in Table 1. Following the CPG as closely as possible, an alternative definition of SAD, SAD_{CPG}, was constructed. This required that subjects have total T less than 300 ng/dL, free T less than 5 ng/dL, and one or more of the suggestive symptoms or two or more of the associated symptoms.

Application of this definition resulted in fewer subjects classified as exhibiting SAD (28 at T2 and 46 at T3, with five subjects contributing positive records at both waves), leading to difficulty in obtaining stable estimates of the odds of SAD_{CPG} as a function of covariates. In limited exploratory analyses, similar results were observed to those detailed in Table 4, with previous history of SAD_{CPG} being associated with an unadjusted OR of 4.2 (1.4–12.3) and an age-adjusted OR of 3.0 (95% CI = 0.8–12.0). Of the 16 subjects exhibiting SAD_{CPG} at T1, 15 experienced remission by T2.

DISCUSSION

This prospective, population-based study of 762 men suggests that SAD is three to four times as likely to be observed in subjects who have previously exhibited SAD as it is in those who have not, although the majority of subjects who exhibit SAD are likely to experience remission over the course of several years. The results further indicate that the likelihood of remission decreases with age and even more with BMI but in many cases exceeds the likelihood that SAD will persist, the meaningful exception being men whose BMI approaches 35 or more, as documented in Figure 2. For MMAS subjects classified as being normal to overweight (BMI < 30), the probability of remission easily exceeded 50%. The use of a generous measure of SAD was shown not to meaningfully affect results; the results suggest that remission would have been more common had a stricter definition (such as the approximation of the CPG) been employed.

Given the variation in serum T levels with age, health status, lifestyle, and calendar time, it has previously been conjectured that the use of SAD might provide a more temporally stable description than do T levels alone. This does not appear to be the case. These results cast doubt on the clinical usefulness of SAD as operationally defined here.

The symptoms widely employed as indicators of SAD are relatively nonspecific and potentially attributable to a host of other conditions (not least of which is aging itself). Five of the eight symptoms were obtained from the CES-D questionnaire. Although previous analyses of MMAS data suggest some association between depression as measured according to CES-D and serum T concentrations,⁵⁰ the epidemiological evidence for an overarching association between T and mood or individual psychiatric symptoms is limited.²⁹ In addition, as has previously been demonstrated,⁴⁰ even a symptom as commonly associated with T decrease as low libido does not typically indicate low T. This is reflected in the fact that the screens most commonly used to indicate androgen deficiency have only

moderate specificity.^{51–53} It is therefore not wholly surprising to observe that a composite construct may gain little reliability by combining measures of T and symptoms obtained from a questionnaire such as that employed in the MMAS.

In the current sample, SAD did not typically progress with time; although T levels declined within the observed sample overall, those with SAD displayed higher T levels at later dates. This suggests that the initial measurements reflecting low T might have been attributable to a transient change in health or behavior. As in other studies, previous analyses have indicated a dramatic role for body composition in the regulation of serum T concentrations;^{48,49} longitudinal analyses also indicate the importance of other factors such as smoking, medication usage, and major life events (e.g., changes in marital status or employment).⁸ In addition, it is likely that some subjects who exhibit SAD at a particular point in time do so through natural variability that is ultimately “corrected” through regression to the mean. The latter possibility underlines the importance of acknowledging day-to-day intrasubject variation in T concentrations when classifying subjects according to a particular cutoff,²⁰ as may be done, for instance, in enrolling subjects in a clinical trial.

Age-related decreases in T concentrations have known and meaningful consequences that are detrimental to the health of aging men, contributing to loss of muscle and bone and to greater risk of injury and disability, although symptoms thought to be directly attributable to T decline do not always demonstrate the hypothesized association with T levels themselves. It is possible that, because symptoms may exhibit threshold associations with T concentrations,¹⁶ observations taken from a population with much lower T would demonstrate stronger association. Although for the purposes of examining the natural history of disease, it is advantageous to obtain a population-based sample, as was done in this study,⁵⁴ a result of having done so is that the majority of subjects who exhibited SAD in this study had total serum T levels exceeding 200 ng/dL. It is possible that SAD status would be more stable in subjects whose T was lower, although (as noted above with respect to SAD_{CPG}) the limited data available on such subjects suggests that this would not be the case.

Some limitations of this study bear acknowledgment. The MMAS data do not include several potential symptoms of low androgens, for instance, osteoporosis. This represents a limited approximation of the CPG-recommended definition of SAD, although the definition of SAD employed here is consistent with that used in previous analyses of MMAS data.

In addition, because of the unavoidable loss of subjects with time, the potential influence of informative missingness on the results cannot be completely discounted. Results for men aged 40 to 70, had they been restricted to data for the T1 to T2 transition alone, would be similar to those reported here. In addition, the results for SAD transitions between T2 and T3 were similar to those between T1 and T2. Finally, subjects at T2 who were followed at T3 appeared to be similar to those who were not captured at T3.

This longitudinal study of a population-based sample, to the authors’ knowledge the first to examine temporal variation in SAD or a similar construct, demonstrates that composite measures of T levels and the symptoms related to low circulating androgens are likely to be

fluid and lack stability over long periods of time. This suggests that SAD represents a transient, rather than a permanent, state for the majority of the general male population and may cast doubt on the use of SAD or similar constructs as proxies for true age-related hypogonadism. Such a finding has significant implications for the management of subjects with SAD, as well as for the conduct of clinical trials evaluating T replacement.

Acknowledgments

The authors are greatly indebted to Dr. Christopher Longcope, who passed away in 2004. For nearly 20 years, he was an indispensable colleague on the MMAS. His scientific expertise and collegiality are missed.

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the author and has determined that none of the authors have any financial or any other kind of personal conflicts with this manuscript. MMAS study design and data collection were supported by the National Institutes of Health (National Institute of Diabetes and Digestive and Kidney Diseases: DK44995, DK51345; National Institute on Aging: AG04673). The analyses described in this manuscript were supported through an unrestricted educational grant to New England Research Institutes, Inc., from GlaxoSmithKline (GSK) Research and Development. REW and RVC are employees of, and hold equity in, GSK.

Author Contributions: TGT drafted the manuscript. RS and TGT performed the statistical analyses. ABA, ABO, and JBM contributed to the design and execution of the MMAS and acquisition of data. All authors contributed to the conception and design of the analysis, contributed to revisions of the manuscript for intellectual content, and approved the final version of the manuscript.

Sponsor's Role: REW and RVC contributed to the conception and design of the analysis, contributed to revisions of the manuscript for intellectual content, and approved the final version of the manuscript.

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Figure 1.

Symptomatic androgen deficiency (SAD) transitions according to Massachusetts Male Aging Study wave (T1, T2, T3). Number and percentage of subjects with and without SAD are shown, conditional on status at the previous study wave. For a given wave, percentages are calculated to include only subjects eligible and currently under observation; the number of subjects ineligible or lost to follow-up are depicted in dark gray boxes. Time is depicted vertically.

Figure 2.

Probability of symptomatic androgen deficiency (SAD) onset or remission, Massachusetts Male Aging Study (MMAS) wave T1 to T2. Model controls for age, body mass index (BMI), time since T1 study visit (displayed for 7.5 years), and previous SAD status. (Onset assumes SAD absent at T1, remission assumes SAD present at T1.) Panels depict estimated probability of onset or remission according to age for a man with BMI-25 kg/m² (A) and according to BMI for a 55-year-old man (B). Point estimates (thick lines) are accompanied by 95% confidence intervals (thin lines). Estimates are obtained from a Generalized Additive Model 44 taking the form of a logistic regression, and allowing for statistical interaction between age and BMI, of which little was observed.

Table 1

Signs/Symptoms of Androgen Deficiency Available in the Massachusetts Male Aging Study (MMAS), Boston, Massachusetts, 1987–2004

Sign or Symptom	MMAS Measure Used as Indicator of Sign or Symptom	Reference Period
Loss of libido *	“How frequently do you feel sexual desire? This feeling may include wanting to have sexual experience (masturbation or intercourse), planning to have sex, feeling frustrated due to lack of sex, etc.”	
Erectile dysfunction *	T1: 13-item composite based on responses to a sexual activity questionnaire ⁴¹ T2, T3: Validated single-item assessment ⁴³	
Depression	Antidepressant medication use	Current
Lethargy †	“I could not get going.”	Previous week
Inability to concentrate †	“I had trouble keeping my mind on what I was doing.”	Previous week
Sleep disturbance †	“My sleep was restless.”	Previous week
Irritability †	“I was bothered by things that usually don’t bother me.”	Previous week
Depressed mood †	“I felt depressed.”	Previous week

* Symptoms suggestive of androgen deficiency according to the Endocrine Society’s Clinical Practice Guideline.²²

† Symptoms associated with androgen deficiency according to the Endocrine Society’s Clinical Practice Guideline.²²

Table 2**Demographic, Health, and Lifestyle Factors of Analytical Sample**

Factor	T1 → T2 (n = 762)	T2 → T3 (n = 391)
Age, n (%)		
< 50	300 (39.4)	16 (4.1)
50–59	273 (35.8)	179 (45.8)
60–69	182 (23.9)	133 (34.0)
70	7 (0.9)	63 (16.0)
Education, n (%) [†]		
< High school graduate	61 (8.0)	21 (5.4)
High school graduate	120 (15.8)	50 (12.9)
Some college	581 (76.3)	316 (81.7)
Marital status, n (%) [†]		
Never married	62 (8.1)	26 (6.7)
Married	592 (77.7)	308 (79.0)
Divorced or separated	93 (12.2)	41 (10.5)
Widowed	15 (2.0)	15 (3.9)
Annual household income, \$ n (%) [†]		
< 40,000	230 (30.9)	83 (22.0)
40,000–79,999	340 (45.6)	139 (36.8)
80,000	175 (23.5)	156 (41.3)
Comorbidity, n (%)		
Hypertension	165 (21.7)	107 (27.4)
Heart disease [†]	61 (8.0)	32 (8.2)
Diabetes mellitus	28 (3.7)	19 (4.9)
Self-assessed health, n (%) [†]		
Excellent	276 (36.3)	155 (39.6)
Very good	290 (38.2)	170 (43.5)
Good	161 (21.2)	55 (14.1)
Fair or poor	33 (4.4)	11 (2.8)
Health trajectory over previous year, n (%) [†]		
Worse	52 (6.8)	34 (8.8)
About the same	578 (76.1)	294 (75.8)
Better	130 (17.1)	60 (15.5)
Prescription medications, n (%)		
0	381 (50.0)	120 (30.7)
1–2	311 (40.8)	181 (46.3)
3–5	63 (8.3)	81 (20.7)
6	7 (0.9)	9 (2.3)

Factor	T1 → T2 (n = 762)	T2 → T3 (n = 391)
Currently working, n (%)	667 (87.5)	292 (74.7)
Current smoker, n (%)	154 (20.2)	32 (8.2)
Alcohol consumption, drinks/d, n (%) [‡]		
< 1	384 (50.8)	207 (52.9)
1–3	224 (29.6)	123 (31.5)
>3	148 (19.6)	61 (15.6)
Body mass index, kg/m ² , mean ± standard deviation	27.1 ± 4.0	27.6 ± 4.2
Sexual partner available, n (%) [‡]	617 (84.2)	285 (82.9)

* Lagged covariate data shown; T1 data for T1 → T2 transitions, and T2 data for T2 → T3 transitions.

[‡] Data were missing for some subjects.

[‡] Previous and current status displayed for T1 → T2 transitions (762 subjects) and T2 → T3 transitions (391 subjects).

Table 3**Components of Symptomatic Androgen Deficiency of Analytical Sample**

Component	T1 (n = 762)	T2 (n = 762)	T2 (n = 391)	T3 (n = 391)
Total testosterone, ng/dL, mean $\pm$ SD	519 $\pm$ 170	455 $\pm$ 155	456 $\pm$ 154	430 $\pm$ 161
Free testosterone, ng/dL, mean $\pm$ SD	13.5 $\pm$ 5.2	10.5 $\pm$ 3.6	10.7 $\pm$ 3.5	7.4 $\pm$ 2.7
Symptoms and signs, n (%)				
Loss of libido	233 (30.6)	313 (41.1)	137 (35.0)	177 (45.3)
Erectile dysfunction	285 (37.4)	322 (42.3)	155 (39.6)	209 (53.5)
Depression	2 (0.3)	5 (0.7)	0 (0.0)	3 (0.8)
Lethargy	215 (28.0)	197 (25.9)	100 (25.6)	79 (20.2)
Inability to concentrate	252 (33.1)	286 (37.5)	142 (36.3)	144 (36.8)
Sleep disturbance	207 (27.2)	248 (32.6)	132 (33.8)	185 (47.3)
Irritability	183 (24.0)	181 (23.8)	82 (21.0)	114 (29.2)
Depressed mood	179 (23.5)	173 (22.7)	87 (22.3)	84 (21.5)

Previous and current status displayed for T1 $\rightarrow$ T2 transitions (762 subjects) and T2 $\rightarrow$ T3 transitions (391 subjects).

SD = standard deviation.

Table 4**Mixed-Effects Regression Results**

Study Variable	Outcome—SAD		
	Base Model [*]	Full Model [†]	Final Model [‡]
OR, P-Value			
Previous SAD status	4.0, <.001	3.5, <.001	3.8, <.001
Years since previous interview	0.9, .70	0.9, .39	0.8, .34
Study wave			
T2	Reference	Reference	Reference
T3	1.4, .48	1.1, .90	1.0, .95
Age (10 years) [‡]	1.7, <.001	1.6, <.001	1.6, <.001
BMI (10 kg/m ²) [‡]	3.7, <.001	3.3, <.001	3.4, <.001
Medications			
1 or 2	1.8, .004	1.6, .04	1.7, .02
3	2.2, .003	1.3, .40	1.7, .10
General health			
Excellent	Reference	Reference	Reference
Very good	1.8, .02	1.5, .10	1.5, .08
Good, fair, or poor	2.1, .01	1.4, .24	1.5, .15
Comorbidities			
Diabetes mellitus	2.6, .04	1.8, .19	—
Hypertension	1.8, .01	1.3, .22	—
Heart disease	1.9, .05	1.5, .26	—

* Odds ratios (ORs) summarizing association between covariates and symptomatic androgen deficiency (SAD), controlling for base model covariates (previous SAD status, years since previous interview, study wave, and age at last interview).

[†] OR summarizing association between covariates and SAD, controlling for all effects included in models.

[‡] Effects quantify multiplicative increases in odds per 10 years of age and 10 kg/m² of body mass index (BMI).