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Non-steroidal anti-inflammatory drug use and levels of estrogens and androgens in men

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Abstract

Objective—Studies suggest that regular use of non-steroidal anti-inflammatory drugs (NSAIDs) may lower estrogen levels in women. However, no large, population-based studies have assessed NSAID/hormone associations in men. Our objective was to examine the association between use of prescription and over-the-counter NSAIDs and levels of estrogens and androgens in men.

Design—The Boston Area Community Health Survey, an observational survey with initial data collection in 2002–2005.

Patients—1,766 men who provided a blood sample and data on recent analgesic use.

Measurements—Adjusted geometric mean levels of androgens, estrogens, SHBG, LH, and FSH for each category of NSAID use and the percent difference in hormone levels for users vs. non-users.

Results—There was no significant association between prescription or over-the-counter NSAID use and any hormone examined after adjustment for potential confounders. For example, geometric mean testosterone levels were 13.8, 13.6, and 14.2 nmol/L in non-users, prescription, and over-the-counter NSAID users, respectively; the corresponding levels for estradiol were 80.3, 70.4, and 79.9 pmol/L. In stratified analyses, however, prescription NSAID use was associated with lower testosterone, estradiol, and estrone levels in obese men and lower testosterone and dehydroepiandrosterone sulfate levels in inactive men.

Conclusions—While overall these data do not provide strong support for an association between NSAID use and hormone levels in men, prescription NSAIDs may decrease levels of certain estrogens and androgens in obese and inactive men.

Keywords

Androgens; Anti-Inflammatory Agents; Non-Steroidal; Cyclooxygenase 2 Inhibitors; Estrogens; Hormones

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INTRODUCTION

Previous studies suggest that women who regularly use non-steroidal anti-inflammatory drugs (NSAIDs) may have lower estrogen levels than non-users.^{1,2} *Potential mechanisms for this association include NSAID-induced inhibition of aromatase or other enzymes involved in hormone metabolism, such as 17 β -hydroxysteroid dehydrogenase type 5 (AKR1C3).*^{3,4} These mechanisms might also be expected to influence hormone levels in men and possibly risk of hormone-sensitive cancers⁵ or other conditions;^{6–8} however, no large, population-based studies have examined NSAID use and sex steroid hormone concentrations in men. We therefore examined the cross-sectional relationship between use of prescription and over-the-counter NSAIDs and concentrations of estrogens, androgens, SHBG, LH, FSH, and the estradiol/testosterone ratio among 1,766 men in the Boston Area Community Health (BACH) Survey.

MATERIALS AND METHODS

Study design and data collection

BACH is an epidemiologic study of symptoms suggestive of urologic disease conducted among 2,301 male and 3,201 female residents of Boston, Massachusetts. Additional details of the study design are described elsewhere.⁹ Briefly, a multistage stratified cluster sampling design was used to recruit approximately equal numbers of participants in pre-specified groups defined by age (30–39, 40–49, 50–59, 60–79), race/ethnicity (black, Hispanic, white) and gender. Data for the current analyses were collected during baseline, in-person interviews conducted in 2002–2005 by trained, bilingual interviewers. Interviews were completed for 63.3% of eligible individuals, and the resulting sample included 1,767 black, 1,876 Hispanic, and 1,859 white participants. A venous blood sample (20 cm³) was obtained during the interview for 1,899 men (83%) and 1,874 women (59%) as close to waking as possible (median time since waking for men was 3 hours 38 minutes). All participants provided written informed consent and the study was approved by the Institutional Review Board of New England Research Institutes.

Analgesic use

Interviewers assessed use of prescription and over-the-counter analgesics during the past four weeks by direct observation/recording of medication labels, as well as participant self-report with prompts of indications and common brand names. We created a three-level variable for use of any prescription NSAID (selective COX-2 inhibitors or non-selective NSAIDs, with or without over-the-counter NSAIDs), use of over-the-counter NSAIDs (aspirin and/or ibuprofen) only, or no NSAID use. COX-2 inhibitors were still widely used at the time of our baseline data collection in 2002–2005, although use decreased sharply in 2004–2005.¹⁰ In additional analyses we estimated associations separately for aspirin, ibuprofen, and acetaminophen. Although acetaminophen is not considered an NSAID, some evidence suggests that it may inhibit COX activity under certain conditions.¹¹

Covariates

We selected covariates to evaluate as potential confounders based on biologic plausibility or evidence of an association with NSAID use and at least one hormone of interest in age- and race-adjusted analyses. Body mass index (BMI) was calculated from measured weight and height and modeled continuously. Waist circumference was measured twice using a standardized protocol, and the average of the two measures was modeled as a continuous variable. Time between waking and blood draw was calculated from self-reported time of awakening and recorded time of blood draw and modeled continuously. Physical activity was assessed using the Physical Activity Scale for the Elderly¹² and was categorized as low

(<100), medium (100–249), or high (≥ 250). Per-capita income was defined as annual household income divided by household size and categorized into lower ($\leq \$6,000$), middle ($\$6,001$ – $\$30,000$), and upper ($> \$30,000$), such that approximately 25, 50, and 25%, respectively, fell into each group. Self-reported health status was measured using the 12-item Short Form Health Survey¹³ and categorized as fair/poor vs. excellent/very good/good. C-reactive protein (CRP) was assayed using an immunoturbidimetric assay as described previously¹⁴ and categorized (<1, 1–3, > 3 mg/L).

Additional categorical variables evaluated included fasting status (fasted <8 hours, fasted ≥ 8 hours, unknown), time of blood draw (before 9am, 9am–noon, noon–3pm, after 3pm), season of blood draw, alcohol intake (none, <1, 1–2, ≥ 3 drinks/day), marital status (married or living with a partner vs. not living with a partner), smoking status (current vs. never/past), binary variables for use of acetaminophen, opiates, statins, cardiac drugs, antihypertensives, H2 blockers, diuretics, or vasodilators during the past four weeks, and binary comorbidity variables. Arthritis, hypertension, cardiovascular disease (CVD), dyslipidemia, and asthma were assessed using the question “Have you ever been told by a health care provider that you have or had...?” Depression was defined as the presence of at least five of eight symptoms on the abridged Center for Epidemiologic Studies Depression Scale.¹⁵

Laboratory assays

Details of the measurement of testosterone, SHBG, dehydroepiandrosterone sulfate (DHEAS), dihydrotestosterone (DHT), estradiol, and LH are described elsewhere.^{16–18} Briefly, testosterone, SHBG, and DHEAS were measured by competitive electrochemiluminescence immunoassay, and LH and FSH were measured by sandwich electrochemiluminescence immunoassay, on the 2010 Elecsys system (Roche Diagnostics). DHT was measured by radioimmunoassay (Diagnostic Systems Laboratories) and estradiol and estrone were measured by liquid chromatography-tandem mass spectrometry assay (ThermoFisher Scientific and Applied Biosystems-MDS Sciex). Lower limits of detection were 0.0694 nmol/L for testosterone, 3 nmol/L for SHBG, 0.00271 μ mol/L for DHEAS, 0.01376 nmol/L for DHT, 9.175 pmol/L for estradiol, 46.2375 pmol/L for estrone, and 0.10 mIU/mL for LH and FSH. To reliably measure estradiol levels in the low range, values < 45.875 pmol/L were calculated by manual integration of chromatograms. The interassay and intraassay coefficients of variation (CV) were $< 8\%$ and $< 5\%$, respectively, for testosterone, $< 3\%$ and $< 3\%$ for SHBG, $< 5\%$ and $< 3\%$ for DHEAS, $< 9\%$ and $< 7\%$ for DHT, and $< 6\%$ and $< 2\%$ for both LH and FSH. The interassay CVs were 16.6%, 9.1%, and 9.3% at 91.9, 188, and 1,367 pmol/L, respectively, for estradiol, and 13.4%, 17.8%, and 8.9% at 93.6, 184, and 1,494 pmol/L, respectively, for estrone. Free testosterone and free estradiol were calculated using the methods of Södergard et al.¹⁹

Statistical analysis

We excluded men with medical conditions or recent use of medications that may influence hormone levels, including human immunodeficiency virus (n=31), hormonal treatments such as androgen or antiandrogen therapy (n=43), or current cancer treatment (n=22). In addition, we excluded 2 men with missing data for all hormones of interest, 27 with outlying values (> 4 standard deviations from the mean) for one or more hormones, 7 with missing data on time between waking and blood draw, and 1 with missing CRP level. After these exclusions, 1,766 men were eligible for our analysis.

All analyses were conducted using SAS 9.2 and SUDAAN 10.0.1. We log-transformed the values for each hormone to improve normality and calculated adjusted geometric means, the percent difference in hormone levels for NSAID users vs. non-users (calculated as $(e^{\beta} - 1) \times 100$), and the p-value for this difference. We then calculated conditional means for each

log-transformed hormone and exponentiated these values to obtain adjusted geometric means.

We adjusted all models for age, race/ethnicity, time between waking and blood draw, fasting status, waist circumference, CRP level, self-reported health status, alcohol intake, marital status, history of arthritis, CVD, dyslipidemia, or hypertension, and current/recent use of statins, cardiac drugs, or antihypertensives. We used multiple imputation to replace missing covariate data with plausible values;²⁰ less than 1% of the data were missing for most variables, with the exception of income which was missing differentially by race/ethnicity. A total of 25 multiple imputations were performed separately by gender and race/ethnicity using all relevant variables. Medication use was not imputed; instead, individuals with missing data on NSAID use or other medications were assumed to be non-users. To account for the sampling design, all analyses were weighted according to the 2000 Census using weights inversely proportional to the probability of selection. This allows estimates to be interpreted as representative of the eligible subpopulation of Boston, Massachusetts.

We additionally stratified by and examined interactions with age (<50 vs. ≥50), BMI (<30 vs. ≥30 kg/m²), waist circumference (≤102 vs. >102 cm), physical activity (low vs. medium/high), and arthritis status, to assess whether the association between NSAID use and hormone levels differed by level of these covariates. We tested for differences in the associations by modeling interaction terms between each potential modifier of interest and a three-level variable for prescription, over-the-counter, or no NSAID use, and calculating the Wald F test.

RESULTS

Characteristics of the study population by NSAID use are presented in Table 1. Prescription NSAID use was reported by 4% of our population, while 42% used over-the-counter NSAIDs only and 54% reported no NSAID use. On average, prescription NSAID users were older and had larger waist circumference and body mass index compared to men with no NSAID use or over-the-counter NSAID use only. In addition, prescription NSAID users were more likely to report fair/poor health, consume ≥3 alcoholic drinks per day, have a history of arthritis, and have a CRP level >3 mg/L, while users of over-the-counter NSAIDs were more likely to have a history of CVD or dyslipidemia. Users of any NSAID (prescription and/or over-the-counter) were more likely to be white and married or living with a partner, and use of cardiac drugs and antihypertensives was highest among prescription NSAID users, intermediate among over-the-counter NSAID users, and lowest among non-users.

There was no clear association between prescription or over-the-counter NSAID use and any hormone examined, after adjustment for multiple potential confounders (Table 2). Levels of estradiol, free estradiol, estrone, and DHEAS were 12–16% lower among prescription NSAID users compared to men with no NSAID use, *and levels of LH were 15% higher among prescription NSAID users*, but these differences were not statistically significant and there was no evidence of associations with over-the-counter NSAID use. Stratified analyses failed to show any clear variation in the results by age (Table 3). Prescription NSAID use was associated with lower levels of estrone among men <50 and DHEAS among men ≥50, compared to men with no NSAID use; however, none of the *P*-values for interaction between NSAID use and binary age were statistically significant.

We observed significant interactions between NSAID use and binary BMI for estrone, *LH*, *and the ratio of estradiol to testosterone*, and borderline significant interactions for estradiol and free estradiol (Table 4). Among obese men (BMI ≥30 kg/m²), prescription NSAID use

was associated with significantly lower levels of free testosterone (-18.7% , $P=0.03$), estradiol (-25.9% , $P=0.01$), free estradiol (-25.4% , $P=0.01$), and estrone (-27.1% , $P<0.001$), borderline significant lower levels of total testosterone (-19.8% , $P=0.06$), *significantly higher levels of LH* (32.7% , $P=0.01$), and *borderline significant higher levels of FSH* (20.1% , $P=0.08$), when compared to men with no NSAID use. None of these hormones were associated with over-the-counter NSAID use in obese men, with the exception of estrone which was 11.1% higher among over-the-counter NSAID users vs. non-users ($P=0.04$). There was no evidence of an association between prescription or over-the-counter NSAID use and any hormone examined among non-obese men. The results were essentially unchanged when adjusted for continuous BMI instead of waist circumference, and were similar but of lesser magnitude when stratified by waist circumference rather than BMI (data not shown).

In addition to BMI, there was also evidence of variation in the association between NSAIDs and hormones by level of physical activity (Table 5). Among men with low levels of activity, prescription NSAID use was associated with significantly lower levels of free testosterone (-13.8% , $P=0.04$) and DHEAS (-34.4% , $P=0.002$) and *significantly higher levels of LH* (46.6% , $P=0.02$), and the P -values for interaction were statistically significant for testosterone ($P=0.03$) and free testosterone ($P=0.02$). There were no statistically significant associations between over-the-counter NSAID use and hormone levels among men with low activity or between prescription or over-the-counter NSAID use and hormone levels among men with medium/high activity, *with the exception of lower FSH levels among over-the-counter NSAID users with medium/high activity* (-9.1% , $P=0.04$).

We additionally examined variation in the results by self-reported history of arthritis, to assess whether the associations with prescription NSAID use might be confounded by arthritis status. There were no statistically significant interactions between NSAID use and arthritis history, and hormone levels tended to be lower among prescription NSAID users without a history of arthritis but not those with a history of arthritis, when compared to men with no NSAID use (data not shown). However, most differences in hormone levels for NSAID users vs. non-users were not statistically significant in either group; the exceptions were estrone, which was 22.5% lower among prescription NSAID users without arthritis ($P=0.01$), DHEAS, which was 26.6% lower among prescription NSAID users with a history of arthritis ($P=0.02$), and FSH, which was 18.2% lower among over-the-counter NSAID users with a history of arthritis ($P=0.03$).

In sensitivity analyses, the inverse associations between prescription NSAID use and levels of certain hormones were stronger in men with early morning blood collection. For example, in men with blood collection before 10am there were significant associations between prescription NSAID use and lower levels of free testosterone (-20.2% , $P=0.01$) and DHEAS (-30.5% , $P=0.003$) and borderline significant associations between prescription NSAID use and lower levels of testosterone (-14.7% , $P=0.08$) and free estradiol (-17.8% , $P=0.08$) (data not shown).

There was no clear evidence of an association with type of over-the-counter NSAID use (aspirin vs. ibuprofen) or acetaminophen use (data not shown). Men who reported using aspirin but not ibuprofen had borderline significant lower levels of free estradiol (-11.4% , $P=0.07$) and LH (-8.5% , $P=0.05$) and *significantly lower levels of FSH* (-12.3% , $P=0.01$), compared to men with no prescription or over-the-counter NSAID use. *There were no statistically significant differences in hormone levels for users of ibuprofen only or aspirin and ibuprofen combined, compared to men with no NSAID use.* Users of acetaminophen only had borderline significant lower levels of SHBG (-8.0% , $P=0.05$), while users of both acetaminophen and over-the-counter NSAIDs had significantly higher levels of estrone

(11.5%, $P=0.02$); however, there was no consistent evidence of an association with acetaminophen use.

DISCUSSION

Our results do not provide strong support for an association between prescription or over-the-counter NSAID use and sex steroid hormone levels in men. Individuals who used prescription NSAIDs within four weeks prior to blood collection had lower levels of several hormones, when compared to those with no NSAID use, but none of the associations reached statistical significance in analyses of all men combined. However, in stratified analyses there was evidence of interactions with BMI and physical activity, including significant associations between prescription NSAID use and lower levels of free testosterone, estradiol, free estradiol, and estrone among obese men and between prescription NSAID use and lower levels of free testosterone and DHEAS among inactive men. Although our results suggest that prescription NSAID use may affect hormone levels in certain subgroups of men, additional studies are needed to confirm these results and to explore potential mechanisms.

To our knowledge, no large, population-based studies have examined associations between NSAID use and sex steroid hormone levels in men. In three studies of analgesic use and hormone levels in postmenopausal women, two studies reported significant associations between use of aspirin or non-aspirin NSAIDs and lower estrogen levels,^{1,2} while the third study reported no association between regular NSAID use and levels of estrogens or androgens.²¹ Several small clinical investigations and one small observational study have examined NSAID use and androgen levels in men. In a study of 12 male athletes, a 10-day course of aspirin treatment was associated with a borderline significant increase in plasma testosterone but no change in DHEAS or free testosterone.²² In contrast, an observational study of 34 healthy young men reported no association between aspirin use and plasma testosterone.²³ In a study of 5 sedentary males, treatment with a single 400 mg dose of propyphenazone was associated with decreased urinary excretion of several testosterone metabolites, but no association was observed for treatment with other NSAIDs.²⁴ Another study of 8 healthy young men reported that aspirin inhibited the increase in plasma testosterone levels typically caused by administration of human chorionic gonadotropin.²⁵ These studies suggest a possible association between NSAID use and androgen levels in men but are limited by inconsistent results, small sample sizes, and the inclusion of a small number of different NSAIDs and hormones.

In the current analysis, we observed evidence of lower estrogen levels but no difference in testosterone levels among prescription NSAID users overall and significantly lower levels of both androgens and estrogens among obese users of prescription NSAIDs. In contrast, aromatase inhibition due to NSAID-induced inhibition of COX and prostaglandin E2 would be expected to result in lower estrogen and higher androgen levels.²⁶ In a study of 12 severely obese men, weekly treatment with 2.5 mg of the aromatase inhibitor letrozole was associated with increased testosterone and decreased estradiol levels,²⁷ suggesting that the differences in our results could be due to a mechanism other than aromatase inhibition. The enzyme AKR1C3 preferentially transforms androstenedione to testosterone,^{3,28} but interestingly in the prostate appears to inactivate DHT.²⁹ AKR1C3 also reduces estrone to the more potent estrogen estradiol and catalyzes the production of pro-inflammatory prostaglandins.³ AKR1C3 expression is elevated in adipose tissue and reduced by weight loss³⁰ and is strongly inhibited by NSAIDs,^{3,31} which may have contributed to our results. The disparate results by obesity status and activity level also could be due to differences in the hormonal profiles, the rate of catabolism of testosterone and estradiol, sensitivity to NSAIDs in certain subgroups of men, or larger amounts of adipose tissue and higher levels

of peripheral aromatization in obese and inactive men. However, it is also possible that the associations observed may be due to non-hormonal mechanisms. For example, lower hormone levels among prescription NSAID users, in particular those who are obese or inactive, may be due to confounding by health status or other characteristics of these individuals. There was no evidence of variation in the NSAIDs/hormones association by arthritis history in our analysis, although it is possible that other preexisting conditions may have influenced both NSAID use and hormone levels. *The results for LH and FSH were generally consistent with the expected negative feedback between gonadotropins and testosterone.*

In addition to the potential for uncontrolled confounding, other limitations of our data include the lack of information on the duration, frequency, and recency of NSAID use. Although our exposure variables capture NSAID use within the past four weeks, use within a few days prior to blood collection may be most relevant for hormone levels. In addition, a relatively small number of men reported current or recent use of prescription NSAIDs, and we were unable to examine associations with different prescription NSAID classes. In our analysis we observed associations between prescription NSAID use and lower levels of several hormones, particularly among obese and inactive men, but no association with use of over-the-counter NSAIDs. The lack of an association with over-the-counter NSAID use could be due to differences in the COX inhibitory activity of prescription vs. over-the-counter NSAIDs or more frequent use among individuals with an indication for prescription NSAIDs. *Further, use of over-the-counter NSAIDs may be reported with less accuracy than prescription NSAIDs. Although medication use was assessed both by self-report and direct observation of medication labels, over-the-counter NSAIDs may be used sporadically and their use may therefore be more difficult to recall. Users of over-the-counter NSAIDs were more likely to report a history of arthritis or cardiovascular disease than non-users, however, suggesting some degree of reliability of their reporting.* The cross-sectional nature of our analysis is also a limitation, as it is impossible to determine the temporal relationship between NSAID use and hormone levels and the potential impact of preexisting conditions or other factors. *We also do not have data on acute illness, which can influence levels of certain hormones. In addition, blood was collected from participants at different times of the day, which may have influenced the results due to diurnal variation in hormone levels. In sensitivity analyses the results were essentially unchanged when adjusted for time of blood collection, but the inverse associations between NSAID use and levels of certain hormones appeared to be stronger when restricted to men with blood collection before 10 am. Finally, testosterone levels were assessed by a platform-based immunoassay that is known to underestimate testosterone levels across the range of concentrations in men and women.³² Such measurement error likely resulted in an underestimate of testosterone levels for both users and non-users of NSAIDs but little change in the percent difference for users vs. non-users.*

Our analysis also has several strengths, such as the large number of men included, the use of community-based sampling, and the racial and socioeconomic diversity of our population. In addition, we have data on multiple hormones of interest and detailed covariate data assessed at the time of blood collection, which allowed us to carefully control for confounding by these variables.

In summary, although we did not observe an association between NSAID use and levels of estrogens or androgens overall, our results suggest a possible association between prescription NSAID use and hormone levels in obese and inactive men. However, additional research is needed to confirm these results and to explore potential mechanisms. If NSAIDs do in fact modulate hormone levels, this could have a large public health impact due to the

common use of NSAIDs and the high prevalence of potentially hormone-related diseases such as type 2 diabetes,⁶ cardiovascular disease,⁸ and prostate cancer.^{5,33,34}

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REFERENCES

1. Gates MA, Tworoger SS, Eliassen AH, et al. Analgesic use and sex steroid hormone concentrations in postmenopausal women. *Cancer Epidemiol Biomarkers Prev.* 2010; 19:1033–1041. [PubMed: 20332258]
2. Hudson AG, Gierach GL, Modugno F, et al. Nonsteroidal anti-inflammatory drug use and serum total estradiol in postmenopausal women. *Cancer Epidemiol Biomarkers Prev.* 2008; 17:680–687. [PubMed: 18349287]
3. Byrns MC, Jin Y, Penning TM. Inhibitors of type 5 17beta-hydroxysteroid dehydrogenase (AKR1C3): Overview and structural insights. *J Steroid Biochem Mol Biol.* 2010
4. Diaz-Cruz ES, Brueggemeier RW. Interrelationships between cyclooxygenases and aromatase: unraveling the relevance of cyclooxygenase inhibitors in breast cancer. *Anticancer Agents Med Chem.* 2006; 6:221–232. [PubMed: 16712450]
5. Kelloff GJ, Lubet RA, Lieberman R, et al. Aromatase inhibitors as potential cancer chemopreventives. *Cancer Epidemiol Biomarkers Prev.* 1998; 7:65–78. [PubMed: 9456245]
6. Ding EL, Song Y, Malik VS, et al. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA.* 2006; 295:1288–1299. [PubMed: 16537739]
7. Brand JS, van der Tweel I, Grobbee DE, et al. Testosterone, sex hormone-binding globulin and the metabolic syndrome: a systematic review and meta-analysis of observational studies. *Int J Epidemiol.* 2011; 40:189–207. [PubMed: 20870782]
8. Ruige JB, Mahmoud AM, De Bacquer D, et al. Endogenous testosterone and cardiovascular disease in healthy men: a meta-analysis. *Heart.* 2010
9. McKinlay JB, Link CL. Measuring the Urologic Iceberg: Design and Implementation of the Boston Area Community Health (BACH) Survey. *Eur Urol.* 2007; 52:389–396. [PubMed: 17383808]
10. Wheeler BW, Metcalfe C, Gunnell D, et al. Population impact of regulatory activity restricting prescribing of COX-2 inhibitors: ecological study. *Br J Clin Pharmacol.* 2009; 68:752–764. [PubMed: 19917000]
11. Graham GG, Scott KF. Mechanism of action of paracetamol. *Am J Ther.* 2005; 12:46–55. [PubMed: 15662292]
12. Washburn RA, Smith KW, Jette AM, et al. The Physical Activity Scale for the Elderly (PASE): development and evaluation. *J Clin Epidemiol.* 1993; 46:153–162. [PubMed: 8437031]
13. Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care.* 1996; 34:220–233. [PubMed: 8628042]
14. Kupelian V, McVary KT, Barry MJ, et al. Association of C-reactive protein and lower urinary tract symptoms in men and women: results from Boston Area Community Health survey. *Urology.* 2009; 73:950–957. [PubMed: 19394490]
15. Turvey CL, Wallace RB, Herzog R. A revised CES-D measure of depressive symptoms and a DSM-based measure of major depressive episodes in the elderly. *Int Psychogeriatr.* 1999; 11:139–148. [PubMed: 11475428]
16. Litman HJ, Bhasin S, Link CL, et al. Serum androgen levels in black, Hispanic, and white men. *J Clin Endocrinol Metab.* 2006; 91:4326–4334. [PubMed: 16912139]

17. Litman HJ, Bhasin S, O'Leary MP, et al. An investigation of the relationship between sex-steroid levels and urological symptoms: results from the Boston Area Community Health survey. *BJU Int.* 2007; 100:321–326. [PubMed: 17506868]
18. Hall SA, Page ST, Travison TG, et al. Do statins affect androgen levels in men? Results from the Boston area community health survey. *Cancer Epidemiol Biomarkers Prev.* 2007; 16:1587–1594. [PubMed: 17684132]
19. Sodergard R, Backstrom T, Shanbhag V, et al. Calculation of free and bound fractions of testosterone and estradiol-17 beta to human plasma proteins at body temperature. *J Steroid Biochem.* 1982; 16:801–810. [PubMed: 7202083]
20. Schafer, JL. Analysis of incomplete multivariate data. New York: Chapman & Hall; 1997.
21. McTiernan A, Wu L, Barnabei VM, et al. Relation of demographic factors, menstrual history, reproduction and medication use to sex hormone levels in postmenopausal women. *Breast Cancer Res Treat.* 2008; 108:217–231. [PubMed: 18297397]
22. Di Luigi L, Rossi C, Sgro P, et al. Do non-steroidal anti-inflammatory drugs influence the steroid hormone milieu in male athletes? *Int J Sports Med.* 2007; 28:809–814. [PubMed: 17497588]
23. Stutz G, Zamudio J, Santillan ME, et al. The effect of alcohol, tobacco, and aspirin consumption on seminal quality among healthy young men. *Arch Environ Health.* 2004; 59:548–552. [PubMed: 16599001]
24. Mazzarino M, Bragano MC, Donati F, et al. Effects of propyphenazone and other non-steroidal anti-inflammatory agents on the synthetic and endogenous androgenic anabolic steroids urinary excretion and/or instrumental detection. *Anal Chim Acta.* 2010; 657:60–68. [PubMed: 19951758]
25. Conte D, Romanelli F, Fillo S, et al. Aspirin inhibits androgen response to chorionic gonadotropin in humans. *Am J Physiol.* 1999; 277:E1032–E1037. [PubMed: 10600792]
26. Czajka-Oraniec I, Simpson ER. Aromatase research and its clinical significance. *Endokrynol Pol.* 2010; 61:126–134. [PubMed: 20205115]
27. Loves S, Ruinemans-Koerts J, de Boer H. Letrozole once a week normalizes serum testosterone in obesity-related male hypogonadism. *Eur J Endocrinol.* 2008; 158:741–747. [PubMed: 18426834]
28. Qiu W, Zhou M, Labrie F, et al. Crystal structures of the multispecific 17beta-hydroxysteroid dehydrogenase type 5: critical androgen regulation in human peripheral tissues. *Mol Endocrinol.* 2004; 18:1798–1807. [PubMed: 15087468]
29. Penning TM, Burczynski ME, Jez JM, et al. Structure-function aspects and inhibitor design of type 5 17beta-hydroxysteroid dehydrogenase (AKR1C3). *Mol Cell Endocrinol.* 2001; 171:137–149. [PubMed: 11165022]
30. Svensson PA, Gabrielsson BG, Jernas M, et al. Regulation of human aldoketoreductase 1C3 (AKR1C3) gene expression in the adipose tissue. *Cell Mol Biol Lett.* 2008; 13:599–613. [PubMed: 18641923]
31. Byrns MC, Penning TM. Type 5 17beta-hydroxysteroid dehydrogenase/prostaglandin F synthase (AKR1C3): role in breast cancer and inhibition by non-steroidal anti-inflammatory drug analogs. *Chem Biol Interact.* 2009; 178:221–227. [PubMed: 19010312]
32. Taieb J, Mathian B, Millot F, et al. Testosterone measured by 10 immunoassays and by isotope-dilution gas chromatography-mass spectrometry in sera from 116 men, women, and children. *Clin Chem.* 2003; 49:1381–1395. [PubMed: 12881456]
33. Williams GP. The role of oestrogen in the pathogenesis of obesity, type 2 diabetes, breast cancer and prostate disease. *Eur J Cancer Prev.* 2010; 19:256–271. [PubMed: 20535861]
34. Platz EA, Giovannucci E. The epidemiology of sex steroid hormones and their signaling and metabolic pathways in the etiology of prostate cancer. *J Steroid Biochem Mol Biol.* 2004; 92:237–253. [PubMed: 15663987]

Table 1

Baseline characteristics of 1,766 men in the Boston Area Community Health Survey by non-steroidal anti-inflammatory drug (NSAID) use*

Covariate	No NSAID use (n=953)	Rx NSAID use (n=72) [†]	OTC NSAID use only (n=741)
Age (mean and standard error [SE])	47.0 (0.6)	48.3 (3.6)	46.8 (0.7)
Body mass index in kg/m ² (mean and SE)	28.3 (0.2)	32.1 (3.5)	28.6 (0.3)
Waist circumference in cm (mean and SE)	96.4 (0.6)	109.8 (9.5)	97.9 (0.8)
Hours from waking to blood draw (<i>median</i>)	3.6	3.9	3.7
Race/ethnicity (%)			
Black	31.6	14.1	19.4
Hispanic	16.6	9.7	10.1
White	51.9	76.2	70.5
Fasting status at blood draw (%)			
Fasted 8+ hours	12.3	11.6	10.0
Fasted <8 hours	55.1	39.2	57.7
Unknown	32.6	49.2	32.3
Fair/poor self-reported health (%)	11.7	23.9	14.6
Alcohol intake (%)			
None	28.3	15.7	24.1
<1 drink/day	39.3	40.5	41.3
1–2 drinks/day	23.4	21.5	26.2
3+ drinks/day	9.0	22.3	8.4
Married or living with partner (%)	50.3	65.7	59.0
History of arthritis (%)	9.8	41.3	20.9
History of cardiovascular disease (%) [‡]	14.0	15.9	23.4
History of dyslipidemia (%)	33.6	30.4	40.8
History of hypertension (%)	22.3	29.3	28.1
Statin use (%)	9.1	16.0	14.7
Cardiac drug use (%)	21.4	36.2	29.8
Antihypertensive use (%)	9.6	22.2	14.8
C-reactive protein level (%)			
<1 mg/L	49.9	38.8	47.2
1–3 mg/L	33.8	18.5	34.4
>3 mg/L	16.3	42.7	18.4
Median (10 th –90 th percentile) hormone levels			
<i>Testosterone, nmol/L</i>	14.5 (8.3–23.5)	13.2 (5.1–25.2)	14.6 (7.7–23.7)
<i>Free testosterone, nmol/L</i>	0.30 (0.19–0.48)	0.24 (0.14–0.70)	0.30 (0.18–0.50)
<i>Estradiol, pmol/L</i>	83.7 (43.3–133)	66.4 (52.5–130)	81.5 (43.7–130)
<i>Free estradiol, pmol/L</i>	2.4 (1.2–3.8)	2.0 (1.7–3.5)	2.3 (1.3–3.7)
<i>Estrone, pmol/L</i>	122 (71.6–213)	102 (82.6–225)	126 (66.1–196)
<i>DHEAS, μmol/L</i>	5.1 (2.1–9.2)	4.0 (1.4–9.9)	5.3 (2.0–10.2)

Covariate	No NSAID use (n=953)	Rx NSAID use (n=72) [†]	OTC NSAID use only (n=741)
<i>DHT, nmol/L</i>	1.3 (0.7–2.9)	1.3 (0.5–3.1)	1.2 (0.7–2.8)
<i>SHBG, nmol/L</i>	29.2 (16.6–54.9)	25.0 (15.2–65.2)	30.2 (16.3–55.0)
<i>LH, IU/L</i>	5.1 (2.7–8.1)	6.4 (3.0–9.1)	4.3 (2.7–8.4)
<i>FSH, IU/L</i>	4.7 (2.4–10.6)	4.2 (2.4–10.9)	4.3 (2.2–10.0)
<i>Ratio of estradiol/testosterone</i>	5.7 (3.3–10.3)	8.1 (3.9–12.0)	5.6 (3.0–11.7)

* Estimates inversely weighted to the probability of selection; percents shown are column percents and may not sum to 100 due to rounding

[†] Use of prescription (Rx) NSAIDs with or without over-the-counter (OTC) NSAIDs

[‡] Defined as a history of coronary artery bypass, angioplasty, myocardial infarction, angina, arrhythmia requiring a pacemaker, heart rhythm disturbance, congestive heart failure, transient ischemic attack, stroke, carotid artery surgery, intermittent claudication, surgery or angioplasty for arterial disease of the leg, pulmonary embolism, aortic aneurysm, deep vein thrombosis, Raynaud's disease, or peripheral vascular disease

Adjusted geometric mean hormone levels by non-steroidal anti-inflammatory drug (NSAID) use among 1,766 men in the Boston Area Community Health Survey*

Table 2

Hormone	N	No NSAID use (n=953)		Rx NSAID use (n=72) [†]			OTC NSAID use only (n=741)		
		Mean	P-value [‡]	Mean	Percent Difference [‡]	P-value [‡]	Mean	Percent Difference [‡]	P-value [‡]
Testosterone (T), nmol/L	1,761	13.8		13.6	-1.5	0.87	14.2	3.1	0.30
Free T, nmol/L	1,760	0.29		0.28	-2.3	0.84	0.30	2.0	0.46
Estradiol (E2), pmol/L	1,500	80.3		70.4	-12.3	0.18	79.9	-0.5	0.89
Free E2, pmol/L	1,495	2.3		2.0	-12.8	0.20	2.3	-0.8	0.81
Estrone, pmol/L	1,427	122		107	-12.7	0.09	122	-0.1	0.98
DHEAS, μmol/L	1,760	4.6		3.9	-16.5	0.06	4.8	3.3	0.38
DHT, nmol/L	1,757	1.3		1.4	9.0	0.51	1.3	1.3	0.77
SHBG, nmol/L	1,760	29.5		30.0	1.8	0.79	30.1	2.1	0.49
LH, IU/L	1,760	4.8		5.5	15.3	0.14	4.6	-4.2	0.18
FSH, IU/L	1,760	4.9		4.9	-0.2	0.98	4.5	-6.9	0.08
Ratio of E2/T	1,495	6.6		6.3	-4.1	0.74	6.5	-0.2	0.98

* Adjusted for age (continuous), race/ethnicity (Black, Hispanic, White), time between waking and blood draw (continuous), fasting status (<8 hours, ≥8 hours, unknown), waist circumference (continuous), C-reactive protein level (<1, 1-3, >3 mg/L), self-reported health status (fair/poor vs. excellent/very good/good), alcohol intake (none, <1, 1-2, ≥3 drinks/day), marital status (married/living with a partner vs. not living with a partner), history of arthritis, cardiovascular disease, dyslipidemia, or hypertension, and current/recent use of statins, cardiac drugs, or antihypertensives

[†] Use of prescription (Rx) NSAIDs with or without over-the-counter (OTC) NSAIDs

[‡] Percent difference and P-value for difference compared to no NSAID use; percent difference calculated using $(e^{\beta}-1) \times 100$

Adjusted geometric mean hormone levels by non-steroidal anti-inflammatory drug (NSAID) use among 1,766 men in the Boston Area Community Health Survey, stratified by age*

Table 3

Hormone	Age <50						Age ≥50											
	No use (n=584)			Rx NSAID use (n=28) [†]			OTC NSAID use only (n=403)			No use (n=369)			Rx NSAID use (n=44) [†]			OTC NSAID use only (n=338)		
	Mean	%	P [‡]	Mean	%	Diff [‡]	Mean	%	Diff [‡]	Mean	%	Diff [‡]	Mean	%	Diff [‡]	Mean	%	Diff [‡]
Testosterone (T), nmol/L	14.0	14.1	0.7	0.95	14.5	3.6	0.37	13.4	13.6	1.4	0.86	13.7	2.7	0.48	0.93			
Free T, nmol/L	0.32	0.32	0.3	0.99	0.33	2.5	0.49	0.24	0.24	-2.7	0.68	0.25	2.7	0.48	0.96			
Estradiol (E2), pmol/L	79.1	62.6	-21.0	0.07	80.3	1.4	0.77	82.1	82.7	0.8	0.94	79.4	-3.3	0.45	0.26			
Free E2, pmol/L	2.3	1.8	-21.7	0.10	2.4	1.1	0.81	2.2	2.2	-0.8	0.94	2.1	-3.2	0.47	0.35			
Estrone, pmol/L	118	95	-19.4	0.04	122	3.9	0.39	131	120	-8.2	0.33	123	-5.8	0.22	0.06			
DHEAS, μmol/L	5.7	5.1	-10.3	0.33	6.1	6.5	0.19	3.2	2.1	-32.1	¶	3.1	-1.4	0.81	0.22			
DHT, nmol/L	1.2	1.5	21.3	0.26	1.3	2.7	0.64	1.3	1.2	-7.2	0.59	1.3	-2.2	0.68	0.25			
SHBG, nmol/L	25.8	26.5	2.6	0.80	26.5	2.7	0.53	37.9	40.7	7.4	0.43	37.8	-0.4	0.91	0.45			
LH, IU/L	4.6	5.8	26.5	0.06	4.4	-5.8	0.11	5.0	5.4	7.5	0.46	5.2	3.8	0.51	0.11			
FSH, IU/L	4.1	4.4	5.3	0.70	3.8	-8.7	0.07	6.5	6.8	5.3	0.64	6.5	-0.4	0.95	0.64			
Ratio of E2/T	6.4	5.1	-19.6	0.20	6.6	2.7	0.59	6.8	7.4	9.1	0.57	6.6	-3.1	0.55	0.25			

* Adjusted for age (continuous), race/ethnicity (Black, Hispanic, White), time between waking and blood draw (continuous), fasting status (<8 hours, ≥8 hours, unknown), waist circumference (continuous), C-reactive protein level (<1, 1-3, >3 mg/L), self-reported health status (fair/poor vs. excellent/very good/good), alcohol intake (none, <1, 1-2, ≥3 drinks/day), marital status (married/living with a partner vs. not living with a partner), history of arthritis, cardiovascular disease, dyslipidemia, or hypertension, and current/recent use of statins, cardiac drugs, or antihypertensives

[†] Use of prescription (Rx) NSAIDs with or without over-the-counter (OTC) NSAIDs

[‡] Percent difference and *P*-value for difference compared to no NSAID use; percent difference calculated using $(e^{\beta}-1) \times 100$

[§] *P*-value for interaction calculated using the Wald *F* test for interaction terms between categorical NSAID use and binary age; adjusted for binary age instead of continuous age

[¶] *P*<0.001

Adjusted geometric mean hormone levels by non-steroidal anti-inflammatory drug (NSAID) use among 1,766 men in the Boston Area Community Health Survey, stratified by body mass index (BMI)*

Table 4

Hormone	BMI <30 kg/m ²						BMI ≥30 kg/m ²											
	No use (n=648)			Rx NSAID use (n=43) [†]			OTC NSAID use only (n=458)			No use (n=305)			Rx NSAID use (n=29) [†]			OTC NSAID use only (n=283)		
	Mean	% Diff [‡]	P [§]	Mean	% Diff [‡]	P [§]	Mean	% Diff [‡]	P [§]	Mean	% Diff [‡]	P [§]	Mean	% Diff [‡]	P [§]	Mean	% Diff [‡]	P [§]
Testosterone (T), nmol/L	15.3		16.2	5.8	0.57	16.0	4.8	0.13	11.2	9.0	-19.8	0.06	11.3	1.3	0.79	0.27		
Free T, nmol/L	0.31		0.34	9.8	0.42	0.33	4.8	0.09	0.25	0.21	-18.7	0.03	0.25	-1.2	0.79	0.11		
Estradiol (E2), pmol/L	80.0		79.3	-0.9	0.91	78.7	-1.6	0.72	79.7	59.1	-25.9	0.01	83.3	4.4	0.44	0.05		
Free E2, pmol/L	2.2		2.3	1.0	0.91	2.2	-1.5	0.74	2.4	1.8	-25.4	0.01	2.4	3.6	0.53	0.05		
Estrone, pmol/L	124		123	-0.6	0.94	118	-4.8	0.25	119	86.6	-27.1	¶	132	11.1	0.04	¶		
DHEAS, µmol/L	4.8		4.0	-17.7	0.13	4.9	2.5	0.51	4.3	3.6	-16.0	0.14	4.5	4.1	0.51	0.70		
DHT, nmol/L	1.4		1.3	-11.6	0.34	1.4	0.3	0.95	1.0	1.2	18.1	0.23	1.0	2.2	0.72	0.21		
SHBG, nmol/L	32.6		31.3	-4.1	0.64	33.1	1.4	0.67	24.6	22.5	-8.6	0.37	25.2	2.5	0.61	0.78		
LH, IU/L	4.9		4.8	-2.3	0.80	4.8	-1.7	0.67	4.6	6.0	32.7	0.01	4.2	-7.0	0.13	0.04		
FSH, IU/L	5.0		4.3	-13.6	0.17	4.6	-6.6	0.22	4.7	5.6	20.1	0.08	4.4	-6.6	0.24	0.18		
Ratio of E2/T	5.9		6.6	13.0	0.42	5.4	-7.4	0.08	7.9	6.5	-17.0	0.19	8.8	11.2	0.07	0.01		

* Adjusted for age (continuous), race/ethnicity (Black, Hispanic, White), time between waking and blood draw (continuous), fasting status (<8 hours, ≥8 hours, unknown), waist circumference (continuous), C-reactive protein level (<1, 1-3, >3 mg/L), self-reported health status (fair/poor vs. excellent/very good/good), alcohol intake (none, <1, 1-2, ≥3 drinks/day), marital status (married/living with a partner vs. not living with a partner), history of arthritis, cardiovascular disease, dyslipidemia, or hypertension, and current/recent use of statins, cardiac drugs, or antihypertensives

[†] Use of prescription (Rx) NSAIDs with or without over-the-counter (OTC) NSAIDs

[‡] Percent difference and P-value for difference compared to no NSAID use; percent difference calculated using $(e^{\beta}-1) \times 100$

[§] P-value for interaction calculated using the Wald F test for interaction terms between categorical NSAID use and binary BMI; additionally adjusted for binary BMI

¶ P<0.001

Adjusted geometric mean hormone levels by non-steroidal anti-inflammatory drug (NSAID) use among 1,766 men in the Boston Area Community Health Survey, stratified by level of physical activity*

Table 5

Hormone	Low activity						Medium/high activity											
	No use (n=236)			Rx NSAID use (n=38) [†]			OTC NSAID use only (n=203)			No use (n=717)			Rx NSAID use (n=34) [†]			OTC NSAID use only (n=538)		
	Mean	%	P [‡]	Mean	%	P [‡]	Mean	%	P [‡]	Mean	%	P [‡]	Mean	%	P [‡]	Mean	%	P [‡]
			Diff [§]			Diff [§]			Diff [§]			Diff [§]			Diff [§]			Diff [§]
Testosterone (T), nmol/L	12.8	12.1	−5.2	0.50	12.2	−4.6	0.37	14.0	15.2	8.6	0.47	14.9	6.5	0.06	0.03			
Free T, nmol/L	0.27	0.23	−13.8	0.04	0.26	−3.4	0.45	0.30	0.34	13.6	0.33	0.31	4.9	0.11	0.02			
Estradiol (E2), pmol/L	79.1	79.7	0.8	0.94	74.7	−5.5	0.40	80.1	75.4	−5.9	0.50	81.0	1.2	0.77	0.39			
Free E2, pmol/L	2.2	2.2	−2.9	0.78	2.1	−4.9	0.43	2.3	2.2	−2.4	0.81	2.3	0.7	0.87	0.38			
Estrone, pmol/L	128	108	−15.2	0.12	123	−3.7	0.56	120	113	−5.8	0.52	122	1.2	0.75	0.32			
DHEAS, μmol/L	4.2	2.8	−34.4	0.002	3.7	−12.9	0.05	4.8	4.5	−6.7	0.56	5.2	8.5	0.05	0.17			
DHT, nmol/L	1.3	1.4	13.2	0.33	1.2	−8.3	0.25	1.3	1.2	−5.8	0.65	1.3	4.6	0.34	0.10			
SHBG, nmol/L	29.6	35.2	18.7	0.12	28.9	−2.4	0.65	29.5	27.8	−5.7	0.49	30.4	3.3	0.34	0.17			
LH, IU/L	4.8	7.1	46.6	0.02	4.5	−6.1	0.42	4.8	4.7	−2.5	0.76	4.6	−3.6	0.27	0.16			
FSH, IU/L	5.1	6.1	19.5	0.26	4.9	−3.9	0.60	4.9	4.3	−11.0	0.26	4.4	−9.1	0.04	0.25			
Ratio of E2/T	7.1	7.1	0.0	1.00	7.4	4.7	0.49	6.4	6.8	5.9	0.74	6.2	−2.8	0.53	0.39			

* Stratified by low (<100) vs. medium/high (≥100) Physical Activity Scale for the Elderly score; adjusted for age (continuous), race/ethnicity (Black, Hispanic, White), time between waking and blood draw (continuous), fasting status (<8 hours, ≥8 hours, unknown), waist circumference (continuous), C-reactive protein level (<1, 1–3, >3 mg/L), self-reported health status (fair/poor vs. excellent/very good/good), alcohol intake (none, <1, 1–2, ≥3 drinks/day), marital status (married/living with a partner vs. not living with a partner), history of arthritis, cardiovascular disease, dyslipidemia, or hypertension, and current/recent use of statins, cardiac drugs, or antihypertensives

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[‡] Percent difference and P-value for difference compared to no NSAID use; percent difference calculated using $(e^{\beta} - 1) \times 100$

[§] P-value for interaction calculated using the Wald F test for interaction terms between categorical NSAID use and binary activity score; additionally adjusted for binary activity score