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Use of non-prescription analgesics and male reproductive function

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ABSTRACT

We studied the association between intake of non-prescription analgesics and semen quality and male reproductive hormone levels in a cross-sectional study among 1493 men. The men provided one semen (n = 1493) and blood sample (n = 1056) and filled in questionnaires on use of non-prescription analgesics (paracetamol, NSAIDs and combination drugs (yes/no)). Adjusting for age, study and other covariates, we observed no association between intake of non-prescription analgesics and markers of semen quality. Adjusting for age and time of day of blood sampling, users of non-prescription analgesics had a 10.4% (95% confidence interval (CI) 4.0–17.1%) higher testosterone level than non-users. When we stratified by medication type, the association between analgesics and higher testosterone was observed between users of non-steroidal anti-inflammatory drugs (NSAIDs) and combination drugs but not paracetamol. This study suggests that use of non-prescription analgesics is associated with slightly higher serum testosterone levels than non-use.

1. Introduction

About 15% of couples trying to conceive do not achieve a pregnancy within one year of unprotected intercourse [1]. Various diseases affect human fertility negatively, but no single cause has been identified to account for the present fecundity problems, although reduced semen quality is a concern.

A considerable proportion of the general population uses non-prescription medication such as paracetamol (also known as acetaminophen) and non-steroidal anti-inflammatory drugs (NSAIDs); and sales of these non-prescription analgesics have increased during the past 20 years [2]. Although paracetamol and NSAIDs are used in substantial quantities throughout the world, the mechanisms by which they act are only partly known. Both compounds are thought to act through cyclo-oxygenase (COX) inhibition which results in inhibition of the prostaglandin synthesis [3]; and this inhibition of prostaglandins is suggested to disturb the masculinization in the prenatal period in mice [4]. However, paracetamol may also act as a cannabinoid (CB_1) activator [5].

An animal study found reduced anogenital distance in male rats prenatally exposed to paracetamol and acetylsalicylic acid [6], which could indicate either anti-androgen or oestrogen effects. Paracetamol has furthermore been related to suppressed testosterone production in mice [7].

In humans, lower sperm motility has been reported in relation to acetylsalicylic acid use [8], and regular use of traditional NSAIDs such as ibuprofen, has been associated with reduced semen quality in a group of patients attending the Andrology and Reproduction Laboratory in Córboda, Argentina [9]. However, as these men suffer from illness, we cannot exclude the risk of confounding by indication.

Another study reported no overall association between exposure to NSAIDs and reproductive hormones however lower levels of oestrogens, testosterone and dihydroepiandrosterone were observed in the subgroup of users of NSAIDs, who also were overweight and physically inactive [10].

The wide exposure through self-medication in the general population and the risk that these non-prescription analgesics may affect human hormones make these drugs potential disturbers of the human endocrine control of the reproductive function. Furthermore, tests of adverse effects on reproductive function are not part of the routine test of new medicines, and therefore the potential effects of medication on fertility is unknown for the vast majority of products and call for studies with information of medicine use and male reproductive function.

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Table 1
Number of participants, participation rates and year of study in the three cohorts.

Study subgroups	Number of Participants[a]	Participation rate[b] (%)	Year of study	Reference
Lead workers	437	18	1996–1997	Bonde et al. [11]
Farmers	256	32	1995–1996	Larsen et al. [12]
Inuendo	800	18	2002–2004	Toft et al. [13]
Total	1493			

[a] Number of participants with information on medicine use and markers of reproductive health.
[b] Participation rate in the original studies.

Our study is to date the largest epidemiological study to examine the association between intake of paracetamol and NSAIDs and semen quality and male reproductive hormones in Greenlandic and European men.

2. Methods

2.1. Study population

From 1995 to 2004, three separate occupational or environmental semen quality studies were conducted by our research group and collaborators. A total of 1493 men participated (Table 1). One study included lead workers from England, Belgium and Italy (the Lead worker study) [11], one comprised Danish farmers (the Farmer study) [12] and one comprised men from the general population in Greenland, Poland, Sweden and Ukraine (the Inuendo study) [13].

The Lead worker and the Farmer studies were both occupational studies investigating semen quality in relation to inorganic lead and pesticides, respectively. The Inuendo study was an environmental study investigating semen quality in relation to environmental organochlorine exposure.

The men were included in the studies if they had: No vasectomy, no known azoospermia and reproductive organ abnormalities. The participation rates varied from 18 to 32%.

The study population in the present study comprises the 1493 men with information on intake of non-prescription medication and markers of semen quality. Only the Farmer and Inuendo studies had information on reproductive hormones (n = 1056). Detailed study descriptions are found in the original publications and characteristics according to original study is presented in Supplementary Table 1.

2.2. Ethical approvals

Ethical approval was obtained for all included studies by local ethical authorities.

2.3. Measures of exposure

Information on use of non-prescription analgesics was obtained from self-completed questionnaires. In the Lead worker and Farmer studies, the men were asked about any use of medication during the past three months and in the Inuendo study, the men were asked about any medicine use during the past six months. Furthermore, participants were asked to specify the medicine name, if any use. Information on dose and duration of use was not reported.

We pooled all analgesics into one group for the main analysis (yes/no) and also stratified it in three sub-groups: paracetamol (yes/no), NSAIDs (including acetylsalicylic acid) (yes/no) and combination drugs (drugs containing a mixture of analgesics and other medications (e.g. paracetamol, NSAIDs and antihistamines)) (yes/no).

2.4. Measures of outcome

The participants produced a semen sample by masturbating into a 50 ml polyethylene jar. The samples were collected at the participants' homes and kept close to the body during transportation to avoid cooling. Semen analysis was performed either in a mobile laboratory or in a hospital laboratory, and 82.3% of the samples were analysed within the first hour after ejaculation. Trained medical laboratory technicians performed the analyses in accordance with the successive editions of the guidelines published by the World Health Organization (1980–1999) in its Laboratory manual for examination of human semen and sperm – cervical mucus interaction [14,15]. Semen volume was measured in a tube with 0.1 ml accuracy or on a balance. Sperm concentration was counted in an improved Neubauer chamber by use of a phase-contrast microscope.

Among the participants in the Farmer and Inuendo studies, blood samples were collected by trained medical laboratory technicians. No blood samples were collected in the Lead study. Serum was stored at −20 or −80° C until analysis.

In the Farmer study, all hormones were analysed using immunometric methods, as earlier described [12]. The lower limits of detection (LOD) of luteinizing hormone (LH), follicle stimulating hormone (FSH) and sex hormone binding globulin (SHBG) assays were 0.05 IU/l, 0.06 IU/l and 0.5 nmol/l, respectively. The coefficients of variation (CV) within and between assays were <10%. The LOD of the testosterone assay was 0.23 nmol/l, and the CV within and between assays were <10%. The LOD for Inhibin B was 0.20 ng/l and the CV within and between assays were <12% and <17%, respectively.

In the Inuendo study, all assays were analysed at Skåne University Hospital (Malmö, Sweden), as earlier described in [16]. The LODs were 0.2 IU/l for LH, 0.2 IU/l for FSH and 8.0 pmol/l for estradiol. The CVs were 2.9%, 2.6% and 8.1%, respectively. The LOD for serum testosterone was 0.35 nmol/l and CV of 2.8% at 2.9 nmol/l and 3.2% at 8.1 nmol/l. The LOD for SHBG was 0.02 nmol/l and the CVs were 5.5% and 4.6%, respectively. The LOD for Inhibin B was 15 ng/l and intra-assay and total assay CV <7%.

2.5. Covariate data

Information on potential confounding factors, including lifestyle, occupational, reproductive and medical information was obtained from the main questionnaires used in the original studies. Information on sexual abstinence and spillage during semen collection was collected from a questionnaire filled in by the participants when delivering the semen sample.

2.6. Statistical analyses

The exposure variables non-prescription analgesics, paracetamol, NSAIDs and combination drugs were dichotomized (yes/no). The outcome variables sperm concentration, semen volume, total sperm count, percentage motile sperm cells (motility), percentage morphologically normal sperm cells (morphology), DNA fragmen-

tation index (DFI), LH, FSH, Inhibin B, SHBG, testosterone and estradiol were continuous. We evaluated the model fit by visual inspection of residuals versus predicted values. To improve normality and homogeneity of variance of the residuals in the tested associations, all outcomes were ln-transformed. Generalized multiple linear regression analysis was used to assess the associations between use of analgesic and the markers of semen quality and reproductive hormones. The main results are pooled analysis of all three study populations. The results from the multiple regression analyses were back-transformed and are presented as percentage differences with 95% confidence intervals (CI) on the original scale.

The multivariate semen models all included age (continuous), and disease in the reproductive organs (including: chlamydia infection, gonorrhea, syphilis, cryptorchidism, epididymitis, mumps in adulthood, orchitis, testicular cyst, testicular cancer and surgery because of varicocele) (yes/no), fever during the past three months (yes/no) and sexual abstinence time (continuous, days). Sperm concentration, motility and morphology were additionally adjusted for spillage during collection of the semen sample (yes/no). Moreover, analysis of motility only included samples analysed within one hour of collection, and total sperm count and semen volume only included samples from individuals reporting no spillage. In analyses of sperm concentration and total sperm count, only samples >0 were included in the models since all exposures were ln-transformed. All pooled models were in addition adjusted for sub-study (categorical).

In the hormone models, age (continuous) and time of the day for sampling (before or after 12 a.m.) were entered as covariates, and all the pooled models were adjusted for sub-study (categorical).

We evaluated potential effect modification of the association between the exposures and outcomes by study sub-group using stratified analysis and by adding interaction terms in the models (e.g. Farmer sub-study*non-prescription analgesics). In supplementary analyses, the exposure-outcome associations are presented stratified by medicine type (paracetamol, NSAIDs and combination drugs). As a sensitivity analysis, the excluded 0 values in sperm concentration (n = 2) and total sperm count (n = 2) were added with 0.5 and motility (n = 2) to keep them in the analyses.

All statistical analyses were performed using STATA 13.1 (StataCorp, College Station, TX, USA).

3. Results

3.1. Characteristics of the study population

Characteristics of the 1493 participants stratified by intake of non-prescription analgesics are presented in Table 2. Compared to non-users (n = 1236) of non-prescription analgesics, users (n = 257) were slightly younger, more often smokers and reported having had fever during the past three months. Furthermore, users less often suffered from diseases in the reproductive organs, and had a shorter time to analysis. The duration of sexual abstinence was 3 days among both users and non-users of non-prescription analgesics. Of the participants using non-prescription analgesics, 27.3% used paracetamol, 50.3% used NSAIDs and 22.5 used combination drugs (Table 2).

3.2. Non-prescription analgesics and markers of semen quality and male reproductive hormones

Unadjusted and adjusted percentage difference of the semen quality and sex hormones in relation to intake of non-prescription analgesics are presented in Tables 3 and 4, respectively. We found no associations between analgesics and semen quality in neither pooled nor stratified (by sub-study) analyses (Table 3).

In pooled analysis, intake of non-prescription analgesics was positively associated with testosterone (adjusted difference (CI) = 10.4% (4.0, 17.1) and also among men from the Inuendo study (adjusted difference (CI) = 12.3% (4.5, 20.7)), but apparently not in the Farmer study (adjusted difference (CI) = 3.7% (−7.0, 15.4)) (Table 4). No significant effect modification by sub-study was indicated except for SHBG with an interaction $p = 0.04$.

Results stratified by type of medication are presented in Supplementary Tables 2–7. No associations were seen between intake of paracetamol (Supplementary Table 2), NSAIDs (Supplementary Table 3) or combination drugs (Supplementary Table 4) and markers of semen quality. No association was present between intake of paracetamol and male reproductive hormones (Supplementary Table 5). In the pooled analyses of intake of NSAIDs and male reproductive hormones, testosterone tended to be higher among men using NSAIDs (adjusted difference (CI) 8.3% (−0.3, 17.7)) (Supplementary Table 6). When stratified by sub-study, the estimates were similar but CIs wider. Use of NSAIDs was associated with lower Inhibin B among men from the Inuendo study which was not consistent through the studies. In the pooled analyses of intake of combination drugs and male reproductive hormones, testosterone was higher among men using combination drugs (adjusted difference (CI) 13.4% (2.5, 25.5)) (Supplementary Table 7).

4. Discussion

In the present study of 1056 men with measured hormone levels, we observed a slightly higher serum testosterone level among users of non-prescription analgesics. The association seemed to be driven mainly through intake of NSAIDs and combination drugs. No associations between intake of non-prescription analgesics and markers of semen quality were observed in the 1493 men with measured semen quality markers.

To our knowledge, only two prior studies have reported on the association between intake of non-prescription analgesics and markers of semen quality. Among 34 young men, who used ≥500 mg of acetylsalicylic acid per week, significantly lower sperm motility was reported as compared to non-use [8]. Authors reported adjustment for alcohol consumption and tobacco smoking but no other possible confounders were considered including time from ejaculation to analysis. Corresponding to the findings by Stutz and colleagues, lower sperm motility was reported in relation to intake of NSAIDs along with lower seminal volume, percentage morphological normal spermatozoa and glucosidase concentration and higher percentage of dead cells in a sample of 1376 patients attending the Andrology and Reproduction Laboratory in Argentina [9].

In a study of 1766 men from the Boston Area Community Health Survey (2002–2005), no overall difference in hormone level in relation to NSAID use was observed. However, when stratified by BMI and activity level NSAID use was associated with lower testosterone and estradiol levels in obese men and lower testosterone and dehydroepiandrosterone sulfate levels in inactive men [10]. We could not test these results as the number of obese men in our study was low (n = 73), and we had no information on activity level. Among the normal weight men in our study, we still observed a positive association between intake of NSAIDs and combination drugs and higher testosterone levels (data not shown). In another study of 18 young men, authors observed no association between intake of acetylsalicylic acid and serum testosterone [8]. Similarly, among 12 moderately trained athletes, no association was observed between intake of acetylsalicylic acid and serum testosterone, albeit acetylsalicylic acid modified the absolute and percentage of variation of testosterone and cortisol and their ratio compared to placebo [17].

Table 2
Characteristics of the study population.

	Non-users of non-prescription analgesics $N = 1236$	Users of non-prescription analgesics $N = 257$
Person related characteristics:		
Age (years)	36.1	34.2
Mean (SD)	(9.3)	(8.9)
Body Mass Index (kg/m^2)[a]	25.8	25.3
Mean (SD)	(3.5)	(3.5)
Smoking (yes)	571	156
Number (%)	(46.2)	(60.7)
Diseases in reproductive organs	264	44
Number (%)	(21.4)	(17.0)
Fever during past three months (>38 °C)	98	36
Number (%)	(7.9)	(14.0)
Semen related characteristics:		
Sperm concentration (10^6/ml)	54.4	52.0
Median (5th-95th percentile)	(8.0–195.0)	(10.0–183.3)
Semen volume (ml)	3.0	3.0
Median (5th-95th percentile)	(1.0–6.6)	(1.3–7.0)
Total count (x10^6)	161.5	165.2
Median (5th-95th percentile)	(15.6–706.9)	(20.4–630.0)
Motile sperm (%)	56.0	58.0
Median (5th-95th percentile)	(19.0–82.0)	(21.0–84.0)
DFI (%)	10.8	11.7
Median (5th-95th percentile)	(4.1–36.1)	(3.8–33.6)
Spillage at sampling	150	26
Number (%)	(12.1)	(10.1)
Time to analysis (minutes)	45	35
Median (5th-95th percentile)	(25–90)	(25–90)
Duration of abstinence (days)	3	3
Median (5th-95th percentile)	(1–10)	(1–7)
Hormone related characteristics		
Luteinizing hormone (IU/l)	3.8	3.8
Median (5th-95th percentile)	(1.9–7.9)	(1.8–8.0)
Follicle stimulating hormone (IU/l)	4.0	4.1
Median (5th-95th percentile)	(1.7–9.9)	(1.7–11.7)
Inhibin B (pg/ml)	179.0	176.0(77.0–314.0)
Median (5th-95th percentile)	(90.0–313.0)	
Sex hormone binding globulin (nmol/l)	29.5	29.9
Median (5th-95th percentile)	(14.5–57.7)	(15.8–49.1)
Testosterone (nmol/ml)	14.3	16.2
Median (5th-95th percentile)	(7.4–24.1)	(8.4–26.0)
Estradiol (pmol/l)	67.8	72.4
Median (5th-95th percentile)	(41.0–112.6)	(48.7–117.0)
Use of analgesics:		
Paracetamol	–	70
Number (%)		(27.3)
NSAIDs	–	129
Number (%)		(50.2)
Combination[b]	–	58
Number (%)		(22.5)
Cohorts:		
Lead workers	364	73
Number (%)	(83.3)	(16.7)
Farmers	212	44
Number (%)	(82.5)	(17.1)
Inuendo	660	140
Number (%)	(82.5)	(17.5)

[a] Among non-users, 8.6% had missing BMI; among users, 9.7% had missing BMI. [b]Drugs with several pharmaceuticals combined.

Both aforementioned studies are limited by the small sample size, and thus, the risk of type 2 error cannot be eliminated.

Our findings concerning elevated testosterone levels among users of NSAIDs and combination drugs correspond with results from an experimental study using fetal testes tissue from induced abortions. The authors reported indomethacin and acetylsalicylic acid exposure to be associated with higher testosterone levels in human ex-vivo gestational week 8–12 fetuses. Corresponding to our results, they observed no association between fetal paracetamol exposure and testosterone levels [18].

Others find oppositely that non-prescription analgesics tend to be associated with reduced testosterone levels both in experimental and human studies. Hence, direct exposure to paracetamol and indomethacin decreased testosterone production in adult human testes explants [19], and intake of paracetamol and acetylsalicylic acid reduced testosterone production in ex-vivo fetal rat testes [6]. Furthermore, testosterone production was inhibited by paracetamol, acetylsalicylic acid and indomethacin in an ex-vivo model on gestational day 14.5 rat testes [20]. Finally, van den Driesche and colleagues reported seven days exposure of paracetamol to be associated with reduced plasma testosterone in castrate host mice bearing human fetal testis xenografts, whereas exposure for one day showed no association [7]. This could indicate that duration of exposure is relevant as could be expected.

The mechanism by which NSAIDs could cause higher testosterone levels is not well established. The prostaglandin inhibition

Table 3
Markers of semen quality regressed on use of non-prescription analgesics among men from three cohorts.

Cohort Outcome	Exposed/*N*	Crude β (95% CI)	Adjusted β (95% CI)[a]	Interaction *p*[b]
Pooled[c]				
Sperm conc (10^6/ml)	252/1465	−1.4 (−13.6, 12.6)	−0.6 (−13.1, 13.7)	0.13
Semen volume (ml)	229/1291	−0.50 (−8.0, 7.6)	−0.53 (−8.0, 7.6)	0.58
Total count (x10^6)	226/1279	1.9 (−12.9, 19.3)	2.3 (−12.8, 20.0)	0.20
Motile sperm (%)	177/1045	3.1 (−4.5, 11.4)	3.5 (−4.4, 12.0)	0.64
Normal cells (%)[d]	–	–	–	–
DFI (%)	232/1333	1.0 (−7.9, 10.7)	3.4 (−5.5, 13.1)	0.35
Lead workers				
Sperm conc (10^6/ml)	70/418	20.0 (−8.6, 57.5)	23.5 (−6.3, 62.9)	–
Semen volume (ml)	67/372	5.0 (−10.3, 22.9)	1.8 (−12.7, 18.7)	–
Total count (x10^6)	66/367	23.4 (−8.9, 67.1)	23.4 (−9.3, 68.0)	–
Motile sperm (%)	24/192	14.6 (−3.3, 35.8)	13.5 (−4.6, 34.9)	–
Normal cells (%)[d]	–	–	–	–
DFI (%)	57/353	12.2 (−6.7, 35.0)	11.8 (−6.3, 33.4)	–
Farmers				
Sperm conc (10^6/ml)	44/254	−10.7 (−34.9, 22.6)	−6.5 (−32.7, 30.0)	–
Semen volume (ml)	41/221	−1.0 (−18.5, 20.2)	4.5 (−13.6, 26.4)	–
Total count (x10^6)	41/219	−12.1 (−40.8, 30.5)	−1.1 (−32.8, 45.4)	–
Motile sperm (%)	18/113	3.8 (−16.4, 28.8)	6.0 (−16.5, 34.5)	–
Normal cells (%)[d]	43/247	−0.40 (−8.4, 8.3)	−0.8 (7.7, 10.0)	–
DFI (%)	43/246	−9.0 (−25.4, 10.9)	−11.7 (−28.0, 8.2)	–
Inuendo				
Sperm conc (10^6/ml)	138/793	−8.0 (−22.4, 9.1)	−10.7 (−25.0, 6.2)	–
Semen volume (ml)	121/698	−3.2 (−12.4, 7.0)	−4.2 (−13.5, 6.2)	–
Total count (x10^6)	119/693	−3.5 (−21.5, 18.6)	8.0 (−25.6, 13.7)	–
Motile sperm (%)	135/740	1.0 (−8.0, 10.9)	1.6 (−7.6, 11.8)	–
Normal cells (%)[cd]	132/775	2.3 (−9.3, 15.4)	2.2 (−9.6, 15.6)	–
DFI (%)	132/734	−0.3 (−12.1, 13.1)	1.7 (−10.0, 14.8)	–

β expresses the percentage difference between those who have used non-prescription analgesics compared to those who have not used it.
Analysis of sperm motility only included samples analysed within one hour of collection, and total sperm count and volume only included samples from individuals reporting no spillage.

[a] All outcomes were adjusted for age (continuous), reproductive diseases (yes/no), abstinence time, days (continuous) and fever during the past three months (yes/no); sperm concentration, motile sperm and normal cells were further adjusted for spillage (yes/no).

[b] Test for interaction between non-prescription analgesics and sub-study in each outcome.

[c] Further adjusted for study sub-group.

[d] Normal cells were measured using WHO year 1992 in the Farmer cohort and WHO year 1999 in the Inuendo cohort.

Table 4
Male reproductive hormones regressed on use of non-prescription analgesics among men from the Farmer and Inuendo studies.

Cohort Outcome	Exposed/*N*	Crude β (95% CI)	Adjusted β (95% CI)[a]	Interaction *p*[b]
Pooled[c]				
LH	167/890	1.1 (−6.1, 8.7)	0.7 (−6.6, 8.6)	0.90
FSH	167/889	1.4 (−7.6, 11.3)	5.7 (−3.5, 15.8)	0.35
Inhibin B	165/884	−3.8 (−10.9, 3.9)	−3.9 (−11.2, 4.0)	0.82
SHBG	167/890	2.8 (−3.8, 9.8)	6.7 (−0.3, 14.1)	**0.04**
Testosterone	167/890	**12.7 (6.0, 19.7)**	**10.4 (4.0, 17.1)**	0.25
Estradiol	167/886	6.4 (−0.8, 14.0)	4.1 (−3.2, 11.9)	0.94
Farmers				
LH	40/246	0.1 (−14.1, 16.6)	0.02 (−14.2, 16.6)	–
FSH	40/246	−0.8 (−17.6, 19.4)	−1.2 (−17.9, 19.0)	–
Inhibin B	39/241	−5.9 (−21.6, 12.9)	−5.1 (−20.7, 13.6)	–
SHBG	40/247	−5.0 (−17.2, 9.0)	−5.4 (−17.4, 8.5)	–
Testosterone	40/246	3.2 (−7.2, 14.9)	3.7 (−7.0, 15.4)	–
Estradiol	40/245	3.3 (−16.4, 27.6)	3.0 (−16.7, 27.3)	–
Inuendo				
LH	127/644	1.4 (−6.7, 10.2)	1.3 (−7.1, 10.5)	–
FSH	127/643	2.1 (−8.4, 13.8)	9.3 (−1.5, 21.3)	–
Inhibin B	126/643	−3.1 (−10.7, 5.2)	−3.2 (−11.2, 5.5)	–
SHBG	127/643	5.5 (−2.2, 13.7)	**11.1 (2.9, 20.0)**	–
Testosterone	127/644	**16.0 (7.8, 24.7)**	**12.3 (4.5, 20.7)**	–
Estradiol	127/641	**7.4 (1.4, 13.7)**	4.0 (−1.9, 10.23)	–

β expresses the percentage difference between those who have used non-prescription analgesics compared to those who have not used it.

[a] Adjusted for age (continuous, years) and time of the day for sampling (before or after 12 a.m.).

[b] Test for interaction between non-prescription analgesics and sub-study in each outcome.

[c] Crude and adjusted pooled analyses are adjusted for cohort.

from NSAIDs may e.g. cause an increase in testosterone production at the gonadal level or through a higher testosterone synthesis but experimental studies need to examine the mechanism.

The present study has some limitations. The participation rate was low in the original studies (18% in the Lead worker and Inuendo studies) which could introduce selection bias in both directions. In

the Lead worker and Farmer studies, some of the men had knowledge of their fertility and since men with reproductive problems are more likely to participate in semen quality studies [21] this may have caused selection bias if more men with reduced semen quality and with higher intake of non-prescription analgesics participated. We believe, however, that participants hardly payed special attention to intake of non-prescription analgesics as the original studies examined occupational and environmental exposures and did not focus on medication.

Information on intake of non-prescription analgesics was self-reported in questionnaires and we have no information on the dose and length of the intake. In addition, the fact that the use of NSAIDs is reported to be two-fold the use of paracetamol could indicate underreporting of paracetamol use. This may have led to misclassification of the exposure variables which could attenuate a true association. Thus, we cannot exclude the possibility that in fact intake of non-prescription analgesic is associated with lower semen quality and studies with more precise exposure information are warranted.

The cross-sectional nature of our study disables possibilities of determining causality between non-prescription analgesic use and semen quality and sex hormone levels and the possible impact of preexisting illness. In addition, as we did not have any information of indication of use, we cannot eliminate the risk of reverse causation since higher testosterone levels may be associated with behaviour that could led to higher intake of non-prescription analgesics. In future follow-up studies of the association between intake of non-prescription analgesics and male reproductive function, it is of great importance to receive accurate information on indication of use, medication type as well as dose and length of intake.

Also, it is suggested that exposure during the prenatal period is a more crucial window of exposure as the gonads and the reproductive capacity are developed during fetal life, and a follow-up study showed a positive association between intake of paracetamol for more than four weeks during pregnancy and increased occurrence of cryptorchidism [22]. Hence, a follow-up study investigating the association between maternal intake of non-prescription analgesics during pregnancy and subsequent reproductive capacity in young men would be of high interest.

Our analysis also has several strengths, such as the large study population and a study population from Greenland and from 7 European countries with a large age span and comparable reproductive outcomes. Furthermore, we have data on conventional markers of semen quality and reproductive hormones and several personal characteristics, the latter enabling us to adjust for important potential confounding factors.

In conclusion, in this cross-sectional analysis, we found that intake of NSAIDs and combination drugs were associated with slightly higher testosterone levels in healthy Greenlandic and European men. Intake of non-prescription analgesics was not associated with other hormones or with common markers of semen quality. Possible misclassification of data on use of analgesics may have attenuated the results and studies with more precise exposure information are warranted.

Author's role

JPB, GT and SBL collected the data. JP, GT, CHRH and BBH contributed to the design, analyses and interpretation of data. BBH further was responsible for statistical analyses and writing the draft version of the manuscript. All authors revised the manuscript and approved the final version for publication.

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Conflict of interest

The authors have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.reprotox.2017.09.004.

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