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Chronic noise exposure and testosterone deficiency — meta-analysis and meta-regression of experimental studies in rodents

Przewlekła ekspozycja na hałas a niedobór testosteronu — metaanaliza i metaregresja wyników badań na gryzoniach

Angel Dzhambov[1], Donka Dimitrova[2]

[1]Faculty of Medicine, Medical University of Plovdiv, Bulgaria
[2]Department of Health Management, Health Economics and Primary Care, Faculty of Public Health, Medical University of Plovdiv, Bulgaria

Abstract

Introduction: Chronic psychological distress can cause suppression of the hypothalamic–pituitary–testicular axis and thus lead to male hypogonadism, which is associated with psycho-social dysfunction, chronic diseases, and as a result, considerable economic costs. Conversely, noise is a prototypal environmental stressor of growing importance, already linked to birth outcomes and diabetes. However, its effects on male testosterone levels have been paid little attention.

Material and methods: This paper reports a systematic review and meta-analysis of experimental studies in rodents, which have examined the effect of chronic noise stress on serum testosterone levels. A systematic search in MEDLINE, EMBASE and the Internet yielded seven studies. A quality effects meta-analytical model was applied to compute pooled Hedges's g. Quality effects meta-regression was carried out as well.

Results: We found pooled Hedges's g of –2.41 (95% CI: –3.28, –1.54), indicating a very large effect of noise exposure on testosterone. Meta-regression confirmed that the overall duration of exposure explained a significant proportion of the variance across individual effect sizes ($Q_{(1)} = 3.95$, $p = 0.047$). However, there was considerable inter-study heterogeneity ($I^2 = 82\%$) and publication bias ($p = 0.016$). After inputting two studies previously thought to be missing, the pooled effect dropped to $g = –1.53$ (95% CI: –3.01, –0.05).

Conclusions: Chronic noise exposure of ≈ 100 dB leads to a significant reduction of serum testosterone in male rodents. Research on humans is highly warranted, especially given the steady trend in Western societies for increasing the burden of both male hypogonadism and noise pollution. **(Endokrynol Pol 2015; 66 (1): 39–46)**

Key words: *hypogonadism; testosterone deficiency; male fertility; noise exposure; noise pollution; rats; quality effects model; meta-analysis*

Streszczenie

Wstęp: Przewlekły stres może powodować stłumienie osi podwzgórze–przysadka–jądra, a przez to prowadzić do hipogonadyzmu u mężczyzn. Zaburzenie to wiąże się z kolei z występowaniem zaburzeń społeczno-psychologicznych, rozwojem chorób przewlekłych, a przez to generuje znaczne obciążenie ekonomiczne. Hałas jest prototypowym środowiskowym czynnikiem stresogennym, którego znaczenie jest coraz bardziej podnoszone i który został ostatnio powiązany z rozwojem cukrzycy i przebiegiem ciąży. Wpływ hałasu na stężenie testosteronu u mężczyzn nie był jednak dotychczas badany.

Materiał i metody: Niniejsza publikacja zawiera systematyczny przegląd danych i metaanalizę wyników badań dotyczących wpływu przewlekłego stresu w związku z ekspozycją na hałas na stężenia testosteronu w surowicy gryzoni. Dokonano systematycznego przeglądu baz danych MEDLINE i EMBASE, uzyskując siedem publikacji. W oparciu o wyniki tych badań dokonano metaanalizy z obliczeneniem wskaźnika wielkości efektu (wskaźnik *g* Hedgesa) oraz metaregresji.

Wyniki: Wartość wskaźnika *g* Hedgesa wyniosła –2,41 (95% CI: –3,28; –1,54), co wskazuje na bardzo silny wpływ ekspozycji na hałas na stężenie testosteronu. Metaregresja potwierdziła, że czas ekspozycji ma istotny wpływ na wariancję poszczególnych wyników badań ($Q_{(1)} = 3,95$; $p < 0,047$). Jednocześnie stwierdzono jednak znaczną zmienność wyników poszczególnych badań ($I^2 = 82\%$) i pewną stronniczość publikacji ($p = 0,016$). Po dodaniu wyników dwóch przypuszczalnie nieuwzględnionych badań wartość ogólnego wskaźnika *g* spadła do –1,53 (95% CI: –3,01; –0,05).

Wnioski: Przewlekła ekspozycja na hałas o natężeniu ≈ 100 dB prowadzi do istotnego zmniejszenia stężeń testosteronu w surowicy gryzoni. Pożądane jest więc prowadzenie podobnych badań u ludzi. Może to mieć szczególne znaczenie w krajach zachodnich, gdzie obserwuje się rosnące obciążenie hałasem w środowisku, ale także stały trend w kierunku rozwoju hipogonadyzmu u mężczyzn. **(Endokrynol Pol 2015; 66 (1): 39–46)**

Słowa kluczowe: *hipogonadyzm; niedobór testosteronu; płodność mężczyzn; narażenie na hałas; szczury; wskaźnik wielkości efektu; metaanaliza*

Angel Dzhambov M.D., Faculty of Medicine, Medical University of Plovdiv, Bulgaria, e-mail: angelleloti@gmail.com

Introduction

Male hypogonadism (HG) is defined as a clinical syndrome caused by androgen deficiency which may adversely affect multiple organ functions and quality of life [1]. It is associated with sexual dysfunction and decreased fertility, cardiovascular and metabolic disorders, low bone mineral density, obesity, psychosocial and cognitive dysfunction among other chronic complications [2]. Four to five million men in the United States alone are testosterone (T) deficient [3], and about 20% of all infertility cases can be accounted for by the male factor, with an additional 30–40% which can be attributed to both male and female factors [4, 5]. It has been projected that in years to come the Western world will face an increasing burden of male HG [6]. Furthermore, due to higher comorbidity among hypogonadal men, this will be associated with considerable economic costs [7].

Although acute everyday stress is physiological, it has been well established that chronic psychological stress can lead to functional hypogonadotropic hypogonadism [8]. One of the most prominent and pivotal environmental and occupational stressors is noise pollution. It has been labelled a 'man-made plague' of the modern world [9]. More than 600 million people in the world are exposed to extreme noise levels in their workplace [10], while in Europe 80 million people are exposed to community noise levels above 65 dB [11]. Besides its auditory effects [12], noise is adversely related to a higher incidence of cardiovascular diseases [13, 14], psychiatric disorders [15], aggression [16], etc. Emerging evidence suggests that noise pollution might be an environmental risk factor for some endocrinological and reproductive problems such as type 2 diabetes mellitus [17] and adverse birth outcomes [18]. However, little is known about its effects on male fertility and reproduction. Research on humans is currently lacking. On the other hand, animal studies have suggested a possible link between chronic noise exposure and T deficiency in males.

There is a strong biological plausibility for possible adverse effects of noise on T secretion. On the one hand, noise processing is closely linked to the neuroendocrine system in the brain (the hypothalamic autonomic system and the pituitary-adrenal system) and may result in destabilisation of its normal homeostasis [19]. It is well known that stress can alter normal neurohormone secretion [20], and noise is regarded a prototypal environmental stressor [15]. Conversely, the hypothalamic–pituitary–testicular axis is particularly vulnerable to chronic stress of different origins [8]. By increasing corticotropin-releasing hormone and beta-endorphins, stress suppresses the gonadotropin-releasing hormone or abates its pulsatile release, resulting in decreased luteinising hormone and T, respectively [8]. Local intratesticular catecholamines are also involved in androgen suppression on a paracrine level [21].

For this reason, it is particularly important to learn from data from animal models in order to design human trials and epidemiological studies on the impact of noise pollution on male hypogonadism. As far as we are aware, currently there is no research ongoing into this topic. Therefore, this study aimed to determine what the effect was of chronic noise exposure on serum T levels in male rodents.

Material and methods

Search protocol

The research question which our systematic review aimed to answer was: 'What is the effect of chronic noise exposure on serum T in male rodents?' Two researchers were presented with this question and carried out a literature search using standardised search protocol and data-extraction forms. No previous systematic reviews on the topic were found in PROSPERO or the internet. After that, MEDLINE (PubMed), EMBASE (ScienceDirect) and the internet were searched for peer-review literature published in English, Spanish or Russian up to 1 June, 2014. Overlapping papers were considered once. The reviewers used the following free-term combinations: 'noise + testosterone', 'ruido + testosterona' and 'шум + тестостерон'. PubMed yielded 71 results, and ScienceDirect — 353 (335 in English and 18 in Spanish). Relevant filters were used in ScienceDirect. The articles were screened on title, abstract, and full-text levels. Experimental models involving animal species other than rodents were not considered, because they are limited and they were only going to inflate additional heterogeneity. Papers assessing the effects of noise on sperm counts alone were excluded as well, as were those dealing with other types of stress exposure. After applying these exclusion criteria, seven studies were included in the final review.

Quality assessment

In addition to the narrative synthesis, the quality of each study was rated according to the following elements and scorings:

I. Study-specific quality elements
   1. Timeframe of the study — reported (1.0), or not reported (0.0)
   2. Research settings — clearly described (1.0), ambiguously described (0.5), or no description (0.0)
   3. Animal subjects — clearly described species, housing conditions and environment (1.0), ambiguous description (0.5), or no description (0.0)
   4. Sample size — justified by power analysis (1.0), not justified statistically, or no information (0.0)

5. Group assignment — random (1.0), not random, or not described (0.0)
6. Description of exposure conditions — clearly described (1.0), ambiguously described (0.5), or no description (0.0)
7. Assessment of T — reliable method (1.0), or unreliable method or not described (0.0)
8. Biological plausibility — highly plausible (1.0), somewhat plausible (0.5), or implausible or insufficient information (0.0)
9. Adjustments for covariates — adjusted for relevant covariates (1.0), or no adjustments (0.0)
10. Statistical methods — clearly described and adequate (1.0), or inadequate/not described or insufficient information (0.0)

II. Review-specific quality elements

1. Access to the full text — yes (1.0), or no (0.0)
2. Statistical data transformations (only those creating bias) — no (1.0), or yes (0.0)
3. Statistical data imputation — no (1.0), or yes (0.0)
4. Inter-rater agreement (Krippendorff's alpha) on study quality — > 0.9 (1.0), 0.8–0.9 (0.75), 0.7–0.79 (0.5), < 0.7 (0.0)

Although somewhat arbitrary, this rating system is based on the experience of the authors with other meta-analyses, and on consultations with Bulgarian experts in endocrinology and environmental hygiene regarding the design of the studies and biological plausibility of the observed effect.

Data-analytic strategy and meta-synthesis

In order to estimate the effect of chronic noise exposure on T levels, we carried out a meta-analysis. Due to its superiority to the commonly used random effects model, we applied the quality effects meta-analytical model [22, 23]. This uses a quality index Q_i (0.00 to 1.00) representing the probability that the judgment of each study is credible. When "all studies are assessed against a list of predefined safeguards against bias …, a study with the maximum score simply has all safeguards in place and one with zero has none" [24]. Then a study-specific composite is generated that takes into consideration study-specific information and its relationship to other studies to redistribute inverse variance weights. Q_i was assigned to each study according to the quality ratings in Table I, where the scores were converted into quality ranks between 0 and 1 by dividing each score by the score of the highest scoring study in the group, so that the 'best' study was ranked 1.00 and those with lower scores were ranked proportionally lower.

Hedges's g was selected as the effect size estimate because it is a more conservative measure than Cohen's d. When needed, additional data transformations were done. Hedges's g for Rajabzadeh et al. [25] was calculated from the reported p-value (e.g. for $p < 0.05$, $p = 0.05$ was used) (http://handbook.cochrane.org/front_page.htm). The corresponding 95% CIs were calculated according to Hedges & Olkin (1985) (cited by Durlak [26]). All T measurements were converted to ng/ml. On-line T converter was used to convert nmol/l to ng/ml (http://www.nebido.com/tools/index.php/en/default/index/conversion-tool).

A meta-regression was conducted in order to determine the explanatory power of the overall duration of noise exposure (in hours) on the effect sizes. We applied the method of moments using David Wilson's SPSS macro MetaReg.sps. However, instead of using the inverse variance weights, we used the quality weights of the studies, calculated by hand according to Doi & Thalib [22, 23].

Heterogeneity was explored using the chi-square test and the quantity of heterogeneity across studies was measured by the I^2 statistic [27]. According to the I^2, heterogeneity was considered mild (< 30%), moderate (31–50%) or high (> 50%) [28]. Sensitivity analysis was performed by assessing the contribution of each study to the summary effect estimate by excluding it and computing pooled Hedges's g for the remaining studies. Funnel plot depicted possible selective publishing, and Egger's regression analysis was used to test for statistically significant asymmetry with evidence of asymmetry based on $P < 0.10$ (one-tailed) to partially compensate for the low power of the test [29]. 'Fail-safe n' determined the number of unpublished studies necessary to reduce the pooled effect size to non-significance. Duval and Tweedie's 'Trim and Fill' analysis was used to impute missing studies and recalculate the pooled effect size. 'Fail-safe n' and 'Trim and Fill' analyses were run under the random effects model due to software constraints.

Effect sizes were considered statistically significant at $p < 0.05$. All analyses were carried out with MetaXL v.1.4 add-in for Excel v. 2010 (www.epigear.com), Comprehensive Meta Analysis v. 2.2.064 (www.meta-analysis) and MetaReg.sps for SPSS v. 19 (http://mason.gmu.edu/~dwilsonb/ma.html).

Results

Narrative description of the studies

Seven studies were included in our systematic review. Their characteristics are presented in Table I. Except for Armario & Castellanos [30], all were carried out in recent years, and all studies were published in peer-reviewed journals. The geographic distribution of the authors' institutions shows that most research centres were outside Europe. Nonetheless, the designs were somewhat similar. Male rats (five studies) or mice (two studies) were allocated

Table I. *Description of the included studies and quality assessment*

Tabela I. *Zestawienie danych pochodzących z badań włączonych do metaanalizy i ocena jakości wyników*

Study	Swami et al. [34]	Vosoughi et al. [31]	Ruffoli et at. [32]	Armario & Castellanos [30]	Saki et al. [33]	Diab et al. [35]	Rajabzadeh et al. [25]
TF	NRE *(0.0)*	NRE *(0.0)*	NRE *(0.0)*	NRE *(0.0)*	September — December 2010 *(1.0)*	NRE *(0.0)*	NRE *(0.0)*
RS	Universiti Sains Malaysia *(1.0)*	Tarbiat Modares University *(1.0)*	NRE *(0.0)*	NRE *(0.0)*	Physiology research center, Ahvaz Jundishapur University of Medical Sciences *(1.0)*	NRE *(0.0)*	NRE *(0.0)*
AS	Male Sprague Dawley rats (200–250 g); normal habitat *(1.0)*	NMRI adult male mice (25–35 g), aged 7–8 weeks; 23 ± 2 ºC, 40–50% humidity, 12 hrs light/dark; standard diet and water *ad libitum (1.0)*	Male Swiss mice aged 8-week; 12 hrs light/dark, 22–24ºC, 50–60% humidity; laboratory chow and tap water *ad libitum (1.0)*	Male Wistar rats, ≈ 300 g, 22ºC, 12 hrs light, food and water *ad libitum (1.0)*	Male Wistar rats, 220 ± 20 g; 22 ± 1ºC, 12 hrs light/dark, tap water and commercial rat food *ad libitum (1.0)*	Mature male albino rats, 150–200 g; diet *ad libitum (0.5)*	Adult male rats, 200 ± 20 g *(0.5)*
SS	Controls: (n = 6) *vs.* exposed (n = 6), no power analysis *(0.0)*	Controls (n = 12) *vs.* exposed (n = 12), no power analysis *(0.0)*	Controls (n = 15) *vs.* exposed (n = 15), no power analysis *(0.0)*	Controls (n = 7) *vs.* exposed (n = 7), no power analysis *(0.0)*	Controls (n = 8) *vs.* exposed (n = 8), no power analysis *(0.0)*	Controls (n = 10) *vs.* exposed (n = 10), no power analysis *(0.0)*	Controls (n = 6) *vs.* exposed (n = 6), NIA on power analysis *(0.0)*
GA	NRE *(0.0)*	Random *(1.0)*	NRE *(0.0)*	NRE *(0.0)*	Random *(1.0)*	NRE *(0.0)*	Random *(1.0)*
DEC	100 dB traffic noise (10 000 Hz) 3 hrs/day for 90 days in chronic exposure gr. *(1.0)*	10 days, 8 hrs/day, 100 ± 2 dB (700–5700 Hz) for exposed, < 50 dB background noise for controls *(1.0)*	White noise 100 dB (0–26 kHz) 6 hrs/day for 6 weeks *(1.0)*	Alarm bell noise (85 dB) + intermittent light 4 hrs/day for 28 days *(0.5)*	White noise 90–120 dB (300-350 Hz), 7 pm-7 am (12 hrs)/day for 50 days *(1.0)*	White noise 100 dB (0–26 kHz), 6 hrs/day for 30 days *(1.0)*	NIA for dB and Hz, 50 days of exposure *(0.0)*
AT	DRG ELISA KIT IBL HAMBURG, GmbH, GERMANY *(1.0)*	ELISA kit (Monobind Inc., USA, Product code Testosterone: 3775–300) *(1.0)*	Kit from Diagnostic Systems Laboratories, Inc. (Webster, TX, USA) *(1.0)*	RIA, dyethyl-ether extraction, rabbit antiserum against testosterone-3-carboximethyloxime-BSA *(1.0)*	ELISA *(1.0)*	ELISA *(1.0)*	ELISA *(1.0)*
BP	Highly plausible *(1.0)*	Highly plausible for long-term effects (35 days after exposure) *(1.0)*	Highly plausible *(1.0)*	Highly plausible *(1.0)*	Highly plausible *(1.0)*	Highly plausible *(1.0)*	Not sufficient information *(0.0)*
ESE*	0.65 ng/mL, SE = 0.04 (controls) *vs.* 0.30 ng/mL, SE = 0.01 (exposed)	3.62 ng/mL, SD = 0.15 (controls) *vs.* 3.32 ng/mL, SD = 0.27 (exposed)	6.65 ng/mL, SD = 4.60 (controls) *vs.* 1.24 ng/mL, SD = 0.54 (exposed)	134 ng/100 ml, SE = 32 (controls) *vs.* 105 ng/100 ml, SE = 7 (exposed)	16.16 nmol/L, SD = 0.49 (controls) *vs.* 7.39 nmol/L, SD = 0.74 (exposed)	0.732 ng/mL, SE = 0.03 (controls) *vs.* 0.434 ng/mL, SE = 0.024 (exposed)	P < 0.05 (controls *vs.* exposed)
AC	None *(0.0)*	None *(0.0)*	None *(0.0)*	None *(0.0)*	None *(0.0)*	None *(0.0)*	None *(0.0)*
SM	Adequate *(1.0)*	Adequate *(1.0)*	Adequate *(1.0)*	Adequate *(1.0)*	Adequate *(1.0)*	Adequate *(1.0)*	NIA *(0.0)*
AFT	Yes *(1.0)*	Yes *(1.0)*	Yes *(1.0)*	Partly *(0.0)*	Yes *(1.0)*	Yes *(1.0)*	Abstract only *(0.0)*
SDT	None *(1.0)*	None *(1.0)*	None *(1.0)*	None *(1.0)*	None *(1.0)*	None *(1.0)*	p-value to Hedges's g; CIs for g *(0.0)*
SDI	None *(1.0)*	None *(1.0)*	None *(1.0)*	None *(1.0)*	None *(1.0)*	None *(1.0)*	None *(1.0)*
IRA	> 0.9 *(1.0)*	> 0.9 *(1.0)*	> 0.9 *(1.0)*	> 0.9 *(1.0)*	> 0.9 *(1.0)*	> 0.9 *(1.0)*	< 0.7 *(0.0)*
OQ	10	11	9	7.5	12	8.5	3.5

NRE — not reported explicitly; NIA — no information available; TF — Timeframe; RS — Research settings,; AS — Animal subjects; SS — Sample size; GA — Group assignment; DEC — Description of exposure conditions; AT — Assessment of testosterone; BP — Biological plausibility; ESE — extracted statistical estimates; AC — Adjustments for covariates; SM — Statistical methods; AFT — Access to the full text; SDT — Statistical data transformations; SDI — Statistical data imputation; IRA — Inter-rater agreement on study quality; OQ — Overall quality; *not included in the quality scoring

Table II. *Sensitivity analysis by excluding each study one at a time and recalculating the pooled effect size*
Tabela II. *Analiza czułości z wyliczeniem wskaźników wielkości efektu po wyłączeniu poszczególnych badań*

	Change in effect size		Change in heterogeneity		
Excluded study	**Pooled Hedges's g**	**95% CIs**	**Cochran's Q**	**p**	**I^2%**
Swami et al. [34]	–2.32	–3.22, –1.43	28.62	< 0.001	82.53
Vosoughi et al. [31]	–2.94	–4.25, –1.64	33.14	< 0.001	84.92
Ruffoli et at. [32]	–2.56	–3.67, –1.45	33.92	< 0.001	85.26
Armario & Castellanos [30]	–2.66	–3.61, –1.71	27.49	< 0.001	81.81
Saki et al. [33]	–1.77	–2.44, –1.11	15.89	0.007	68.54
Diab et al. [35]	–2.30	–3.24, –1.37	28.32	< 0.001	82.34
Rajabzadeh et al. [25]	–2.39	–3.31, –1.47	33.67	< 0.001	85.15

to control and experimental groups. The sample sizes in both groups were equal and ranged from six to 15. All subjects were hosted in a standard environment. Controls received no noise exposure, while experimental groups were exposed to approximately 100 dB; only Armario & Castellanos [30] used 85 dB. The period of noise exposure ranged from 10 to 90 days, with a mean exposure of about 43 days. Noise frequency however varied considerably. Due to limited full-text access, for the study of Rajabzadeh et al. [25] we imputed the exposure based on previous work of the authors with a similar design. It should be noted that for the meta-analysis we considered only those experimental groups which did not receive other interventions, and disregarded combined exposures of noise and formaldehyde vapour [31], diazepam [32], vitamins C and E [33] or honey and vitamin E [25]. However, for Armario & Castellanos [30], we had to include the combined effect of noise and light exposures, which should be borne in mind. As we were interested in both chronic exposure and long-term effects, we extracted data for the groups with longest exposure, and for Vosoughi et al. [31] we considered the measurements taken on the 35th day after discontinuation of the exposure. All studies used validated and reliable methods (ELISA, RIA) to measure serum T levels. Some carried out histomorphological and microscopic analyses on the testes, assessed sperm parameters or pregnancy in female rats [31–34], but those outcomes were outside this study's scope.

As is evident from Table I, the biological plausibility for the observed effect in each study was high. This refers to also Armario & Castellanos [30], in whose study the overall exposure was low and the noise intensity was only 85 dB, which probably caused the non-significant effect.

Meta-analysis and meta-regression

Given that the study of Saki et al. [33] received the highest quality score, the quality indices of all other studies were computed in comparison to it. From Figure 1, the pooled effect size was g = –2.41, suggesting a very large effect; that is, the exposed group had serum T levels more than two standard deviations lower than those in the control group.

In order to examine the contribution of each study to the overall effect size, we carried out sensitivity analysis by excluding each one at a time (see Table II). Considerable changes were not observed in either the pooled Hedges's g or the heterogeneity, except when Saki et al. [33] was excluded, which resulted in a two-fold drop in the effect and some decrease in the heterogeneity.

As a supplementary analysis, we conducted a meta-regression with the effect size as a dependent variable and the overall duration of noise exposure (hours a day*days of exposure) as an independent variable. The overall duration of noise exposure explained a significant proportion of the variability across effect sizes ($Q_{(1)} = 3.95$, $p = 0.047$) and about 34% (R^2) of the between-study variance (which was 82% according to the I^2 value). The unstandardised beta coefficient was B = –0.01 (SE = 0.01), 95% CI: –0.02, –0.0002. The residual Cochran's Q (11.55, df = 6) was not statistically significant (p = 0.073), and the quality effects variance component was 10.48. These figures suggest that longer exposure to noise is associated with a significant increase in the negative effect on serum T levels.

Publication bias

Given the surprisingly large observed effect, we assessed the possibility of selective publishing, or of some studies having been omitted from our systematic search. Firstly, Egger's regression intercept was significant (B0 = –4.55, 95% CI: –8.52, –0.57, $t_{(5)} = 2.94$, p = 0.016) suggesting the presence of publication bias (see Fig. 2). Secondly, Duval and Tweedie's 'Trim and Fill' analysis suggested that under the random-effects model two studies are missing to the right of the mean effect. When the pooled effect is recalculated after their imputation, it is still significant — g = –1.53 (95% CI:

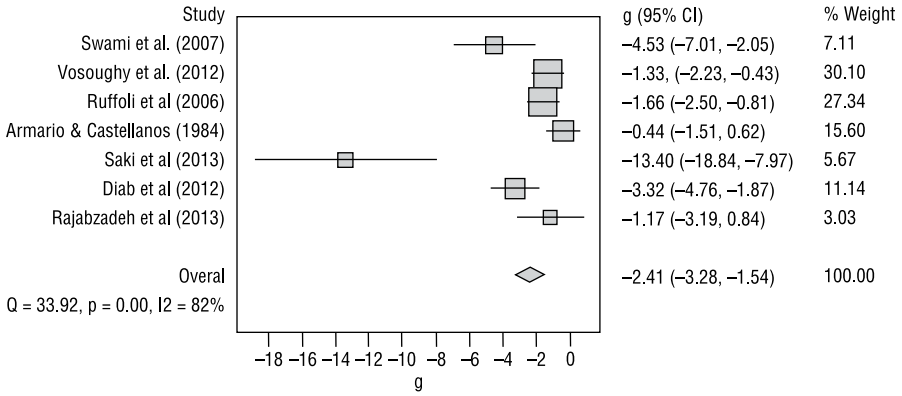

Figure 1. *Forest plot on the effect of chronic noise exposure on serum testosterone. g — Hedges's g; Q, p and I^2 — measures of heterogeneity; each square represents individual study effect size with corresponding confidence intervals*

Rycina 1. *Wykres leśny (forest plot) wpływu przewlekłej ekspozycji na hałas na stężenia testosteronu w surowicy. g — wskaźnik g Hedgesa; Q, p oraz I^2 — wykładniki heterogenności. Każdy kwadrat odpowiada wielkości wskaźnika efektu pojedynczego badania, z podaniem odpowiednich wartości przedziałów ufności (confidence interval)*

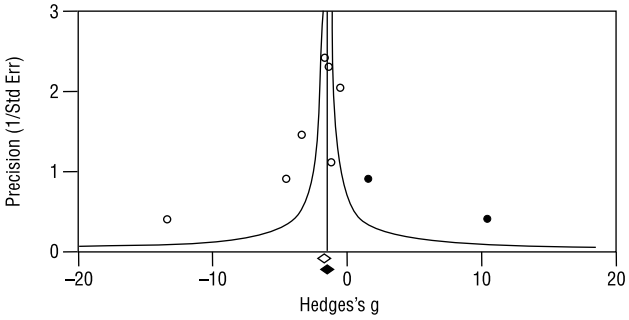

Figure 2. *Funnel plot assessing publication bias for the seven studies included in the meta-analysis. The black circles are the studies which are hypothesised to be missing from our analysis and the white circles are the observed studies*

Rycina 2. *Wykres lejkowy (funnel plot) przedstawiający stronniczość publikacji (publication bias) dotyczących siedmiu badań eksperymentalnych, których wyniki włączono do metaanalizy. Białe koła oznaczają badania rzeczywiście włączone do analizy, a czarne koła — badania, których brak założono w niniejszej analizie*

–3.01, –0.05) — but reduced. To address the concern that some non-significant studies are missing from the analysis, a 'fail-safe N' test was performed. This indicated that 19.6 missing studies would have to be identified for every observed study for the effect to be nullified ($p > 0.05$).

Discussion

Overall findings

Our results suggest that chronic noise exposure of about 100 dB statistically significantly decreases serum T levels in male rodents (rats and mice). Moreover, the negative effect is more pronounced when the overall duration of exposure is longer. It should also be noted that more than a two-fold decrease of T levels in exposed rodents might not be too pessimistic, and the 'true effect' might not be much smaller. On the one hand, the studies that are predicted to be missing from our analysis, and the reduced pooled effect after they have been imputed, indicate overestimation of the effect. This might be due both to selective publishing and/or to our limited access to repository information. On the other hand however, for Rajabzadeh et al. [25] we took a cautious approach as recommended by the Cochrane Handbook by assuming a p-value of 0.05, whereas in fact it was reported as $p < 0.05$ and was therefore significant.

Limitations

The study of Fathollahi et al. [36] which deals with the effects of noise-induced stress on male rat fertility and T levels, although meeting inclusion criteria was not included because its design (same timeframe, description of animals and exposure, aims, findings and scientific writing) are exceptionally similar to those of Saki et al. [33]. This fact creates a doubt that the two papers are actually reporting different studies. Besides, in the acknowledgments, Saki et al. [33] state: "This paper is issued from the thesis of Ali Fathollahi", which supports our concerns regarding a possible unit-of-analysis error if both studies were analysed. We chose to include Saki et al. [33] because of the journal in which it is published (Noise & Health) and the more thorough reporting. There are possibilities to combine groups from the same study [37], but this is not the case here. We should, however, mention that after 12 hrs/day and 50 days of exposure to 90–130 dB of male Wistar rats, Fathollahi et al. [36] found serum T of 3.49 in the exposed group and 8.89 in the control group (no standard deviations

or measurement units are reported). The PhD thesis of Chandralekha [38] also could not be retrieved in full text; it reported a significant reduction in T after 90 days of 3 hrs/day exposure to 100 dB (cited by Fathollahi et al. [36]).

Thus it is evident that almost all published research on the topic points to a significant reduction in T levels after chronic exposure to noise. However, the abovementioned are not the two studies which are allegedly missing to the right of the mean effect size. In the short time available for correspondence, an attempt to contact some authors in order to clarify the uncertainties was made, but to no avail. Finally, the study of Rajabzadeh et al. [25] reports a significant reduction in T levels after noise exposure, but due to the conservative approach that we adopted due to information on the p-value only, in our meta-analysis the 95% CIs overlap zero.

From a statistical point of view, there are several further limitations. Firstly, critics might consider the number of included studies insufficient for meta-analysis. But according to Davey et al. [39], about 75% of all meta-analyses in the relevant medical fields include 5 or 6 studies per meta-analysis. These observations are based on a review of 22,453 meta-analyses from the Cochrane database. Another problem with only seven studies is carrying out a meta-regression. The recommendation of having at least ten studies for each study-level variable in the meta-regression might be overly conservative; therefore the rule of thumb of at least six studies per variable was applied in this meta-regression [40]. Egger's publication bias test might also be considered underpowered, but given that the test was statistically significant, the smallish sample size should not be a problem. It is controversial that we used the quality indices for the meta-regression instead of inverse variance weights, as originally intended by Wilson's MetaReg.sps macro. The data transformations and imputed exposure parameters for the study of Rajabzadeh et al. [25] are a source of bias, but this was reflected in the quality index of the study, which was the lowest, and the weights were redistributed away from it.

Future research

To the best of our knowledge, this was the first study to have attempted to synthethise the accumulated evidence for the negative effect of chronic noise exposure on T. Although it has some limitations, our findings are in line with the conclusions of almost all individual studies. Although we found evidence for selective publishing, it is highly unlikely that the effect will be nullified if the missing papers can be located. Based on these inferences, we suggest that a new line of research is warranted with human participants given the fact that both noise pollution and hypogonadism are projected to increase in years to come. The effects of noise on the cardiovascular system have been well documented [13, 14], but the endocrine system is another possible candidate target. It has already been established that noise pollution might be related to type 2 diabetes [17]. If future experimental and epidemiological studies find that male hypogonadism or T deficiency are determined to some extent by noise pollution, this would have a huge impact on future noise policy, especially given the fact that low T is frequently found in diabetic males [41]. Therefore noise might be impairing the cardiovascular and endocrine systems on different interrelated levels, potentiating each other's pathophysiological mechanisms.

Conclusions

Chronic noise exposure of ≈ 100 dB leads to a significant reduction of serum testosterone in male rodents. The longer the overall exposure, the larger the negative effect becomes. Based on these findings, research on humans is highly warranted, especially given the steady trend in Western societies for increasing the burden of both male hypogonadism and noise pollution.

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