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THE IMPACT OF NOCTURIA ON MORTALITY: A SYSTEMATIC REVIEW AND META-ANALYSIS

Hypothesis / aims of study

Nocturia (waking from sleep at night to void) is one of the most common and bothersome urinary symptoms [1]. Nocturia is associated with impaired quality of life, and is a significant cause of sleep disruption. Several studies have shown that nocturia increases risk of fractures and falls, but it may also be associated with increased mortality. Individuals with nocturia tend to be older and are more likely to suffer comorbidities that may increase risk of death, including obesity, hypertension, coronary heart disease, and obstructive sleep apnea [2]. Possible bidirectional causality between nocturia and such comorbidities necessitates careful adjustment of confounders for reliable estimates of the independent association of nocturia and death. We conducted a systematic review and meta-analysis, assessing the strength, consistency, and potential for bias among pooled associations from all available longitudinal studies.

Study design, materials and methods

We systematically searched PubMed, Scopus, and CINAHL through to February 28, 2014 without language restrictions. In addition, we searched AUA, EAU, ICS and IUGA annual meeting abstracts 2005-2013. We included longitudinal studies assessing nocturia at baseline with death as an endpoint. We applied strict criteria to carefully choose eligible studies and employed standardized, piloted data forms for data collection. We assessed design features that could potentially bias the estimates (risk of bias). These include comparability and representativeness of source populations (sampling frame), confidence in the assessment of nocturia and deaths, adjustment for confounding and missing data. We considered studies that did not provide estimates adjusted or stratified at least for age, as under-adjusted. We considered studies that provided estimates adjusted for falls and/or fractures, which may lie on the causal pathway between nocturia and mortality, as potentially over-adjusted. Random effect meta-analyses were conducted using the metan command, and metaregression was conducted using the metareg command for Stata 12.0.

Results

We screened 3686 abstracts and retrieved 22 full texts. 9 trials enrolling 28,366 participants with more than 240 thousand person years of follow up, provided data. Of these 9 trials, seven, reporting hazard ratios (HR) and 95% confidence intervals could be included in meta-analysis (see Figure).

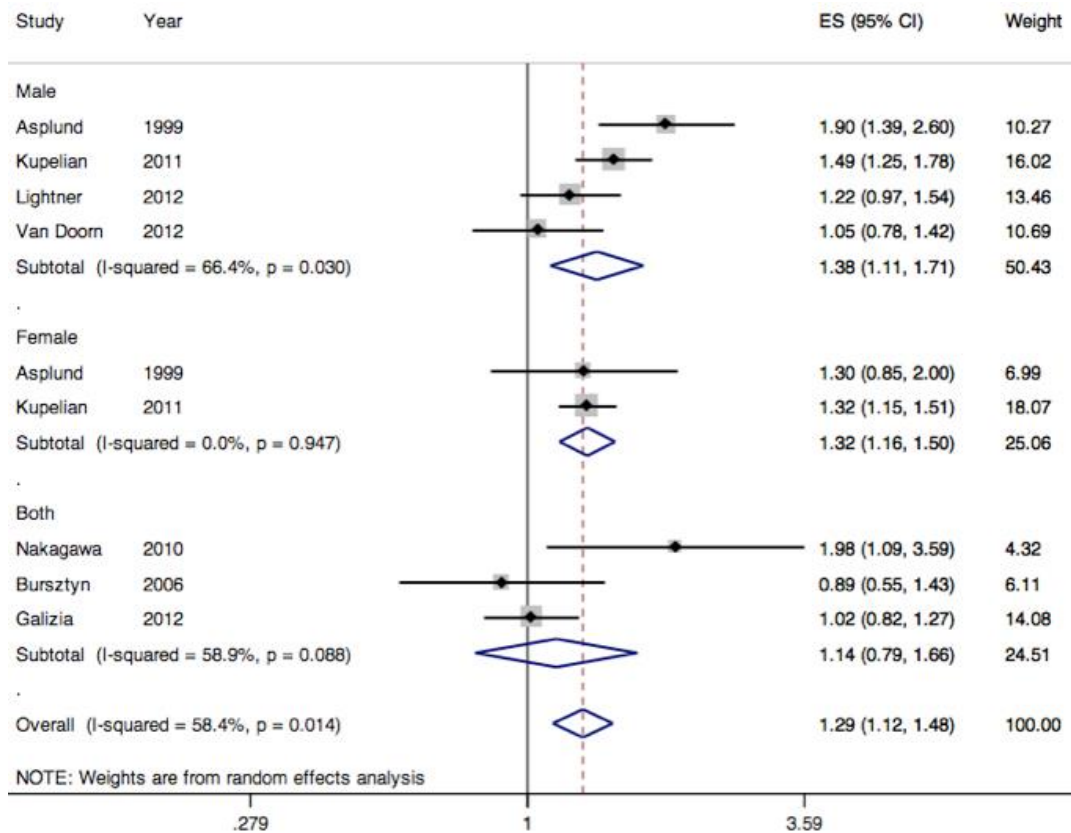


Figure: Forest plot of included studies stratified by gender of study or reported subgroup.

The pooled HR for studies or subgroups of men was 1.35 (95%CI 1.07-1.70, $p=0.011$, $I^2=72.7\%$). The pooled HR for studies or subgroups of women was 1.32 (95%CI 1.16-1.50, $p<0.001$, $I^2=0.0\%$). The pooled HR for studies or subgroups of both genders was 1.14 (95%CI 0.79-1.66, $p=0.48$, $I^2=58.9\%$). The overall pooled HR for participants of either gender was 1.28 (96%CI 1.11-1.47, $p=0.001$, $I^2=60.8\%$). There were only small differences in the main estimate when excluding the single under-adjusted study (pooled HR=1.23), the single over-adjusted study (pooled HR=1.34), or both (pooled HR=1.29). We explored heterogeneity using meta-regression of length of follow up, mean sample age, sample gender, and risk of bias as predictors. The overall meta-regression model performance was good (adjusted $r^2=97.1\%$) with evidence of a difference in association with length of follow up ($p=0.01$), and suggestive evidence of a smaller association among women ($p=0.077$), but no difference by mean sample age ($p=0.206$), or study risk of bias ($p=0.221$). There was no evidence of publication bias (Egger test $p=0.976$).

Interpretation of results

We found consistent evidence of increased mortality for men or women with nocturia, equivalent to 28% excess risk per year. This pooled estimate did not vary substantially when accounting either for the age of included samples or for the degree of adjustment possible in the primary studies. Nonetheless these estimates may still be subject to confounding or unmeasured bias. We found reduced estimates of the association among studies with longer follow up, which may reflect the highly fluctuating nature of nocturia [3].

Concluding message

Evidence from available longitudinal studies consistently demonstrates excess risk of death among men or women with nocturia. Clinicians should be aware that nocturia may be an important marker of ill health. The mediators of the association between nocturia and death should be carefully explored, and the impact of treatment for nocturia on healthy ageing should be tested.

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