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META-ANALYSIS

Resting heart rate and the risk of type 2 diabetes: A systematic review and dose–response meta-analysis of cohort studies

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Abstract *Background:* High resting heart rate has been associated with increased risk of type 2 diabetes in several studies, but the available data are not consistent and it is unclear if there is a dose–response relationship between resting heart rate and type 2 diabetes risk. We aimed to clarify this association by conducting a systematic review and meta-analysis of published studies.
Methods and results: PubMed, Embase and Ovid Medline databases were searched for prospective studies published up until October 11th, 2013. Summary relative risks were estimated using a random effects model. Ten cohort studies with >5628 cases and 119,915 participants were included. The summary RR for high vs. low resting heart rate was 1.83 (95% CI: 1.28–2.60, $I^2 = 88\%$, $n = 7$), and in the dose–response analysis the summary RR was 1.20 (95% CI: 1.07–1.34, $I^2 = 93\%$, $n = 9$) for an increase of 10 beats per minute. The heterogeneity was to a large degree explained by two studies. There was evidence of nonlinear associations between resting heart rate ($p_{\text{nonlinearity}} < 0.0001$) and risk of type 2 diabetes.
Conclusion: The current meta-analysis indicates a strong positive association between high resting heart rate and the risk of type 2 diabetes. As a non-invasive marker of type 2 diabetes risk, resting heart rate may have potential in the clinical setting, especially for interventions aimed at lowering the risk of type 2 diabetes. Additional studies are needed to clarify the mechanisms that may be responsible for the assoiation between resting heart rate and type 2 diabetes.

Introduction

Several previous epidemiological studies have linked elevated resting heart rate to increased risk of cardiovascular disease and all-cause mortality [1,2]. Resting heart rate is known to be a sensitive indicator of the autonomic nervous system [3], and it is possible that an imbalance between parasympathetic and sympathetic activity might contribute towards the observed association between a raised resting heart rate and type 2 diabetes. Increased sympathetic tone not only elevates resting heart rate, but also amplifies insulin resistance [4], which might suggest an intermediary role for impaired autonomic nervous activity in the relationship between resting heart rate and type 2 diabetes. Alternatively, metabolic syndrome, abdominal obesity and insulin resistance may activate the

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sympathetic nervous system, with elevated heart rate being a consequence rather than a cause of the metabolic alterations [5].

Despite this, the association between elevated resting heart rate and type 2 diabetes remains unclear [6–17]. Some studies suggested an increased risk of type 2 diabetes with higher heart rate [6,7,10,12–17], whereas others found the association to be no longer significant after adjustment for potential confounding factors [8,9,11]. These studies were, however, largely heterogeneous with regards to the strength of the association; some reported a 60–100% increase in the risk [6,7,13–15] and others up to a 5-fold increase [14] in risk with elevated heart rate.

Hence, we conducted a systematic review and meta-analysis of prospective studies that examined the relationship between resting heart rate and type 2 diabetes. Specifically we aimed to: 1) clarify the strength of the association, 2) determine whether there is a dose-response relationship, and 3) establish whether the association varies by adjustment for potential confounding factors and other study characteristics.

Methods

Search strategy

We searched the electronic databases PubMed, Embase and Ovid Medline up until October 11th 2013 for prospective studies of resting heart rate and type 2 diabetes risk. We used the following search terms for the search: ("resting heart rate" OR "heart rate" OR "resting pulse") AND "diabetes" with search fields "title/abstract" and "MeSH terms". No language restrictions were imposed. We also examined the reference lists of the studies included in the analysis in an effort to identify additional potentially relevant studies. All retrieved citations were screened by 2 independent reviewers (D.A. and B.H.) and any disagreements were resolved by consensus among authors.

Study selection

Studies were included in the analyses based on the following inclusion criteria: the study had to: 1) have a prospective cohort, case-cohort or nested case–control design from the general population (no studies of high-risk patients with hypertension or cardiovascular disease were included), 2) investigate the association between resting heart rate and risk of type 2 diabetes, 3) present estimates of the relative risk (RR), such as hazard ratios, risk ratios, or odds ratios with the 95% confidence intervals (95% CI), and 4) for the dose–response analysis, a quantitative measure of the heart rate and the total number of cases and person-years or participants had to be available in the publication. We contacted the authors of two studies [6,7] to obtain more detailed results so the studies could be included in the dose–response analysis, and received more detailed data from one study [6].

Data extraction

We extracted the following data from each study: The first author's last name, publication year, country where the study was conducted, the study name, follow-up period, sample size, gender, age, number of cases, exposure by subgroup, resting heart rate level, RRs and 95% CIs for the association and variables adjusted for in the analysis.

Statistical methods

We used random effects models to calculate summary RRs and 95% CIs for the highest vs. the lowest level of resting heart rate and also for the dose–response analysis [18]. The average of the natural logarithm of the RRs was estimated and the RR from each study was weighted by the inverse of its variance and then un-weighted by a variance component which corresponds to the amount of heterogeneity in the analysis. A two-tailed $p < 0.05$ was considered statistically significant. For the two studies which reported results separately for men and women [14] or by treatment group [10], we combined the results using a fixed-effects model to obtain an overall estimate which was used for the main analysis.

The method described by Greenland and Longnecker [19] was used for the dose–response analysis and study-specific slopes (linear trends) and 95% CIs from the natural logs of the RRs and CIs were computed across categories of resting heart rate. This method requires that the distribution of cases and person-years or non-cases and the level of resting heart rate and RRs with the variance estimates for at least three quantitative exposure categories are known. We estimated the distribution of person-years in studies that did not report these. For one study we divided the total number of participants by four to get the approximate number of participants for each quartile [11]. For four studies [11–13,15] we multiplied the mean or median duration of follow-up by the number of participants in each category to get an estimate of the number of person-years for each category. Importantly, because these estimated numbers are only used as starting points for the glst-iterations they do not affect the estimated dose–response slopes (we also repeated the analyses using slightly different numbers of person-years, but this led to identical results). The median or mean resting heart rate level in each category was assigned to the corresponding relative risk for each study. When resting heart rate was reported as ranges we estimated the midpoint for each category by calculating the average of the lower and upper bound. When the highest or lowest category was open-ended or had extreme upper cut-off points we assumed the open-ended interval length to be the same as the adjacent interval. A potential nonlinear dose–response relationship between resting heart rate and type 2 diabetes was examined using fractional polynomial models [20]. We determined the best fitting second order fractional polynomial regression model, defined as the one with the lowest deviance. A likelihood ratio test was used