

Resting heart rate and all-cause and cardiovascular mortality in the general population: a meta-analysis

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ABSTRACT

Background: Data on resting heart rate and risk of all-cause and cardiovascular mortality are inconsistent; the magnitude of associations between resting heart rate and risk of all-cause and cardiovascular mortality varies across studies. We performed a meta-analysis of prospective cohort studies to quantitatively evaluate the associations in the general population.

Methods: We searched PubMed, Embase and MEDLINE from inception to Jan. 1, 2015. We used a random-effects model to combine study-specific relative risks and 95% confidence intervals (CIs). We used restricted cubic spline functions to assess the dose–response relation.

Results: A total of 46 studies were included in the meta-analysis, involving 1 246 203 patients and 78 349 deaths for all-cause mortality, and 848 320 patients and 25 800 deaths for cardiovascular mortality. The relative risk with 10 beats/min increment of resting heart rate was 1.09 (95% CI 1.07–1.12) for all-cause mortality and 1.08 (95% CI 1.06–1.10) for cardiovascular mortality. Compared with the lowest

category, patients with a resting heart rate of 60–80 beats/min had a relative risk of 1.12 (95% CI 1.07–1.17) for all-cause mortality and 1.08 (95% CI 0.99–1.17) for cardiovascular mortality, and those with a resting heart rate of greater than 80 beats/min had a relative risk of 1.45 (95% CI 1.34–1.57) for all-cause mortality and 1.33 (95% CI 1.19–1.47) for cardiovascular mortality. Overall, the results did not differ after adjustment for traditional risk factors for cardiovascular disease. Compared with 45 beats/min, the risk of all-cause mortality increased significantly with increasing resting heart rate in a linear relation, but a significantly increased risk of cardiovascular mortality was observed at 90 beats/min. Substantial heterogeneity and publication bias were detected.

Interpretation: Higher resting heart rate was independently associated with increased risks of all-cause and cardiovascular mortality. This indicates that resting heart rate is a predictor of all-cause and cardiovascular mortality in the general population.

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Resting heart rate is a familiar, straightforward and inexpensive-to-measure clinical variable, and it can be modified by a number of factors, such as physical activity, psychologic stress, smoking, intake of omega-3 fatty acids and medications.^{1–4} Higher heart rate has been linked to increased risks of cardiovascular disease and premature mortality through a multitude of actions, including its detrimental effects on progression of coronary atherosclerosis, on occurrence of myocardial ischemia and ventricular arrhythmia, on left ventricular function and on circulating levels of inflammatory markers.^{5–7} However, measurement of resting heart rate has not been recommended in American and European guidelines on risk assessment of cardiovascular disease.^{8,9} The major reasons for this may be that the magnitude of risk with each increment of higher resting heart rate has been inconsistent among studies, and that rest-

ing heart rate may not be an independent predictor because higher heart rate coexists with traditional risk factors of cardiovascular disease.^{10–13} In addition, data are lacking on the dose–response relation between resting heart rate and all-cause and cardiovascular mortality,^{5,9} although a previous review showed a continuous increase in risk with resting heart rate above 60 beats/min.⁵

Therefore, we conducted a meta-analysis of prospective cohort studies involving the general population, following the MOOSE checklist,¹⁴ to assess the risk of all-cause and cardiovascular mortality associated with each increment of 10 beats/min; to evaluate the possible dose–response relation by restricted cubic spline functions and by pooling risks of all-cause and cardiovascular mortality for comparable categories of resting heart rate (60–80 beats/min and > 80 beats/min); and to evaluate the effect of

traditional risk factors of cardiovascular disease on the association of resting heart rate with risk of all-cause and cardiovascular mortality.

Methods

Literature search and selection

We searched PubMed, Embase and MEDLINE from inception to Jan. 1, 2015, restricting the search to studies involving humans and published in English or Chinese. Details of the search strategy are shown in Appendix 1 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.150535/-/DC1). We reviewed the reference lists from retrieved articles to search for further relevant studies.

Studies were included if they met the following criteria: the study group was the general population (i.e., excluding studies in disease-specific populations); the exposure of interest was resting heart rate; the outcome of interest was all-cause or cardiovascular mortality; age- or multivariate-adjusted relative risk estimates with 95% confidence intervals (CIs) were provided; and the study used a prospective design. If data were duplicated in more than 1 study, we included the study with the longest follow-up duration. Two investigators (D.Z. and X.S.) independently conducted the literature search and selection.

Data extraction

The same 2 investigators independently extracted the following data from each study: the first author's last name, publication year, follow-up duration, country or region where the study was performed, number of participants and deaths, method of resting heart rate assessment, use of heart rate-lowering medication at baseline, variables adjusted for in the analysis and relative risk estimates with corresponding 95% CIs for each category of resting heart rate.

For dose-response analysis with restricted cubic spline models, we extracted the number of deaths and participants (person-years) and relative risk (95% CI) for each category of resting heart rate. For each study, the median level of resting heart rate for each category was assigned to each corresponding RR estimate. If the upper boundary of the highest category was not provided, we assumed that the boundary had the same amplitude as the adjacent category. We extracted relative risk estimates that reflected the greatest degree of control for potential confounders.

Statistical analysis

Pooled measurement was calculated as the inverse variance-weighted mean of the logarithm of relative risk for an increment of 10 beats/min in resting

heart rate. We used a random-effects model to combine study-specific relative risks, which considers both within-study and between-study variation.¹⁵ The I^2 test was used to assess heterogeneity.¹⁶ We conducted meta-regression and subgroup analysis to explore potential sources of heterogeneity and perform comparisons between groups, and we calculated p values from meta-regression with a permutation test of 1000 to control spurious findings.¹⁷ A sensitivity analysis was performed, with one study removed at a time to assess whether the results could have been affected markedly by a single study. We evaluated publication bias using the Egger regression asymmetry test.¹⁸ When publication bias was detected, we adopted the trim-and-fill method to adjust the meta-analysis. This method first “trims” the smaller studies, causing funnel plot asymmetry, and estimates the true “centre” of the funnel with the trimmed funnel plot, and then replaces the omitted studies and their missing “counterparts” around the centre (filling).¹⁹ In addition, we pooled relative risks for comparable categories of resting heart rate (60–80 beats/min and > 80 beats/min) as compared with the lowest category. We assessed study quality using the 9-star Newcastle-Ottawa Scale.²⁰

To assess the dose-response relation, we performed a 2-stage random-effects dose-response meta-analysis,²¹ taking into account between-study heterogeneity. In the first stage, a restricted cubic spline model with 3 knots at the 25th, 50th and 75th percentiles²² of the levels of resting heart rate was estimated using generalized least-square regression, taking into account the correlation within each set of published relative risks.²³ We then combined study-specific estimates using the restricted maximum likelihood method in a multivariate random-effects meta-analysis.²⁴ A p value for nonlinearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to 0. We used 45 beats/min (the lowest value in the included studies) as the reference. In addition, 70 beats/min was then adopted as the reference to examine the potentially protective effect by lower values of heart rate (45–69 beats/min). All statistical analyses were performed with STATA version 12.0. All reported probabilities (p values) were 2-sided, with $p < 0.05$ considered significant.

Results

Search results and study characteristics

After a review of titles and abstracts of the records identified through the literature search, 185 potentially eligible records were identified. After a review of the full texts, 139 records were excluded (Appendix 1). Of the 46 prospective

Table 1: Characteristics of studies included in the meta-analysis

Study	Country/ region	Age, yr (sex)	No. patients (type of mortality)	Follow- up, yr	Resting heart rate assessment	Study quality*
Gillum et al., 1991 ²⁵	US	61.6 (men) 62.5 (women)	Men: 2774 (all-cause: 776; CVD: 373) Women: 3221 (all-cause: 544; CVD: 265)	10.1	Palpation	8
Sandvik et al., 1993 ²⁶	Norway	49.7 (men)	1960 (all-cause: 271; CVD: 144)	16	ECG	7
Mensink et al., 1997 ²⁷	Germany	40–80 (both)	Men: 1827 (all-cause: 205; CVD: 85) Women: 2929 (all-cause: 207; CVD: 68)	12	ECG	7
Benetos et al., 1999 ²⁸	France	51.1 (men) 52.1 (women)	Men: 12 123 (all-cause: 2036; CVD: 664) Women: 7263 (all-cause: 610; CVD: 180)	18.2	ECG	7
Greenland et al., 1999 ²⁹	US	39.8 (men) 40.1 (women)	Men: 18 787 (all-cause: 3384) Women: 14 994 (all-cause: 1693)	22	ECG	9
Palatine et al., 1999 ³⁰	US	72.7 (men)	763 (all-cause: 408; CVD: 200)	12	Palpation	6
Kristal-Boneh et al., 2000 ³¹	Israel	45.6 (men)	3537 (all-cause: 135; CVD: 57)	8	ECG	6
Reunanen et al., 2000 ³²	Finland ³	30–59 (both)	Men: 5598 (all-cause: 1848; CVD: 1033) Women: 5119 (all-cause: 840; CVD: 426)	23	ECG	7
Nilsson et al., 2001 ³³	Sweden	49.6 (men) 43.7 (women)	Men: 22 444 (all-cause: 1902; CVD: 727) Women: 10 902 (all-cause: 397; CVD: 85)	17 12	A device while measuring BP	9
Seccareccia et al., 2001 ³⁴	Italy	40–69 (men)	2533 (all-cause: 350; CVD: 133)	8.5	ECG	6
Cheng et al., 2002 ³⁵	US	40.8 (men)	27 459 (all-cause: 724; CVD: 205)	13.0	ECG	8
Kado et al., 2002 ³⁶	US	71.7 (women)	9702 (all-cause: 1947)	8.9	Palpation	6
Chang et al., 2003 ³⁷	US	78 (women)	942 (all-cause: not reported)	3	ECG	5
Hozawa et al., 2004 ³⁸	Japan	60.3 (both)	1780 (CVD: not reported)	10	A device while measuring BP	7
Okamura et al., 2004 ³⁹	Japan	49.6 (men) 50.0 (women)	Men: 4640 (all-cause: 875; CVD: 291) Women: 5906 (all-cause: 731; CVD: 276)	16.5	ECG	8
Fisher et al., 2006 ⁴⁰	Australia	83.2 (both)	179 (all-cause: 97)	5	A device while measuring BP	5
Savonen et al., 2006 ⁴¹	Finland	54 (men)	1378 (all-cause: 146; CVD: 56)	11.4	ECG	8
Theobald et al., 2007 ⁴²	Sweden	37.6 (men) 33.3 (women)	Men: 490 (all-cause: 120) Women: 499 (all-cause: 84)	26	Palpation	7
Adabag et al., 2008 ⁴³	US	36 (men)	12 555 (all-cause: 4642)	25	ECG	8
Hansen et al., 2008 ⁴⁴	Multiple	56.2 (both)	6928 (all-cause: 850; CVD: 325)	9.6	Palpation	5
Kizilbash et al., 2008 ⁴⁵	US	38.4 (men) 36.3 (women)	Men: 3918 (CVD: 496) Women: 8664 (CVD: 527)	32	ECG	8
Tverdal et al., 2008 ¹³	Norway	41.4 (men) 41.4 (women)	Men: 180 353 (all-cause: 5056; CVD: 1283) Women: 199 490 (all-cause: 3895; CVD: 460)	12	A device while measuring BP	8
Mai et al., 2009 ⁴⁶	China	47 (both)	9856 (all-cause: 1523)	16.2	ECG	7
Batty et al., 2010 ⁴⁷	UK	40–69 (men)	1183 (all-cause: 940)	40	Unclear	5
Cooney et al., 2010 ¹²	Finland	43.3 (men) 43.0 (women)	Men: 10 519 (CVD: 266; all-cause: 806) Women: 11 334 (CVD: 96; all-cause: 408)	12	Palpation	8
Nauman et al., 2010 ⁴⁸	Norway	46 (men) 46 (women)	Men: 24 999 (CVD: 2566) Women: 25 089 (CVD: 1814)	18.2	Palpation	7
Jensen et al., 2011 ⁴⁹	Denmark	49.8 (both)	16 516 (all-cause: 8709; CVD: 3821)	21.2	ECG	8
Jouven et al., 2011 ⁵⁰	France	48.0 (men)	6101 (all-cause: 1635; CVD: 435)	25	Palpation	6
Legeai et al., 2011 ⁵¹	France	73.9 (both)	7147 (all-cause: 615; CVD: 110)	6	A device while measuring BP	5
Nabi et al., 2011 ⁵²	UK	61 (both)	5936 (all-cause: 170)	5.6	ECG	5
Nauman et al., 2011 ⁵³	Norway	51.9 (both)	29 325 (all-cause: 3038)	12	Palpation	9
Inoue et al., 2012 ⁵⁴	Japan	59 (both)	2583 (all-cause: 454; CVD: 153)	12.0	A device while measuring BP	7
Leistner et al., 2012 ¹⁰	Germany	55.9 (both)	5320 (all-cause: 137; CVD: 22)	5	A device while measuring BP	6
Woodward et al., 2012 ⁵⁵	Asia-Pacific region	51 (both)	112 680 (all-cause: 6086; CVD: 2055)	7.4	Unclear	6
Jensen et al., 2013 ⁵⁶	Denmark	62.6 (men)	2798 (all-cause: 1082)	16	ECG	7
Johansen et al., 2013 ⁵⁷	Denmark	64.4 (both)	653 (all-cause: 80)	6.3	ECG	7
Pittaras et al., 2013 ⁵⁸	US	58 (men)	18 642 (all-cause: 5100)	10	ECG	7
Plichart et al., 2013 ⁵⁹	France	44.6 (men) 44.9 (women)	Men: 141 533 (all-cause: not reported) Women: 84 755 (all-cause: not reported)	5	ECG	6
Saxena et al., 2013 ⁶⁰	US	44.0 (both)	53 322 (all-cause: 3125; CVD: 1081)	15.0	ECG	8
Aladin et al., 2014 ⁶¹	US	53.0 (both)	56 634 (all-cause: 6255)	11.1	Unclear	7
Floyd et al., 2014 ⁶²	US	76 (both)	1991 (all-cause: 1326)	12	ECG	7
Hisamatsu et al., 2014 ⁶³	Japan	48.7 (both)	8807 (CVD: 617)	24	ECG	7
Ho et al., 2014 ⁶⁴	US	55 (both)	4058 (all-cause: 1186; CVD: 252)	19	ECG	7
Ó Hartaigh et al., 2014 ⁶⁵	US	43 (both)	2865 (all-cause: 246)	23	Palpation	6
Ryu et al., 2014 ⁶⁶	Korea	66.2 (men)	2600 (all-cause: 1990; CVD: 337)	20.8	Palpation	7
Wang et al., 2014 ⁶⁷	China	51.1 (both)	92 562 (all-cause: 1589)	4	ECG	7

Note: BP = blood pressure, CVD = cardiovascular disease, ECG = electrocardiogram.
*Study quality was judged based on the Newcastle–Ottawa Scale (range 1–9 stars).

Table 2: Pooled results on resting heart rate and risk of all-cause mortality

Variable	60–80 beats/min				> 80 beats/min				10 beats/min increment			
	No.	RR (95% CI)	I ² value, %	p value	No.	RR (95% CI)	I ² value, %	p value	No.	RR (95% CI)	I ² value, %	p value
Age-adjusted	16	1.21 (1.14–1.29)	65.4		17	1.66 (1.48–1.87)	83.9		20	1.14 (1.09–1.18)	97.5	
Multivariate-adjusted	25	1.12 (1.07–1.17)	66.7		32	1.45 (1.34–1.57)	81.3		35	1.09 (1.07–1.12)	92.3	
Excluding deaths during the first 6 mo to 5 yr									12	1.09 (1.06–1.13)	85.9	
Among those not taking heart rate–lowering medication									12	1.11 (1.06–1.16)	95.3	
Among studies adjusting for heart rate–lowering medication									8	1.13 (1.07–1.19)	94.4	
Follow-up duration				0.5				0.01				0.08
> 10 yr	15	1.11 (1.04–1.18)	76.0		18	1.34 (1.22–1.48)	82.5		27	1.08 (1.06–1.10)	90.5	
≤ 10 yr	10	1.14 (1.08–1.20)	0.00		14	1.64 (1.51–1.78)	40.7		8	1.14 (1.07–1.22)	93.4	
Sample size				0.1				0.8				0.8
> 10 000	10	1.07 (1.02–1.13)	67.2		12	1.43 (1.30–1.57)	83.4		15	1.10 (1.06–1.14)	96.0	
≤ 10 000	15	1.17 (1.08–1.27)	55.0		20	1.48 (1.29–1.70)	80.3		20	1.08 (1.06–1.10)	78.3	
Mean age, yr				0.3				0.8				0.03
> 50	16	1.15 (1.08–1.22)	59.5		19	1.46 (1.33–1.60)	73.8		18	1.13 (1.09–1.17)	90.6	
≤ 50	9	1.08 (1.00–1.16)	72.5		13	1.44 (1.24–1.66)	87.5		17	1.07 (1.04–1.09)	92.2	
Region				0.2				0.5				0.04
Europe	14	1.18 (1.10–1.27)	55.2		17	1.52 (1.33–1.74)	83.3		18	1.09 (1.06–1.11)	87.7	
United States	7	1.04 (0.99–1.10)	59.1		9	1.39 (1.22–1.57)	80.2		9	1.05 (1.03–1.08)	85.8	
Asia	3	1.05 (0.84–1.30)	70.6		4	1.35 (1.11–1.64)	70.3		6	1.13 (1.07–1.19)	62.5	
Mixed	1	1.17 (1.04–1.31)	–		1	1.54 (1.43–1.66)	–		2	1.25 (1.01–1.56)	95.2	
Australia	–	–	–		1	1.19 (0.45–3.16)	–					
Excluding CVD at baseline				0.2				0.07				0.6
Yes	16	1.10 (1.03–1.16)	72.9		18	1.36 (1.24–1.50)	82.8		23	1.09 (1.06–1.12)	92.2	
No	9	1.15 (1.09–1.21)	0.00		14	1.60 (1.42–1.80)	70.3		12	1.11 (1.07–1.15)	92.0	
Sex				0.9				> 0.9				0.1
Male	12	1.13 (1.06–1.21)	68.6		14	1.47 (1.27–1.71)	89.0		14	1.08 (1.05–1.11)	91.6	
Female	4	1.06 (0.96–1.19)	26.7		7	1.39 (1.18–1.65)	59.7		9	1.07 (1.04–1.10)	76.5	
Both sexes	9	1.13 (1.03–1.24)	73.5		11	1.44 (1.31–1.59)	68.0		12	1.14 (1.08–1.20)	95.6	
Resting heart rate assessment				> 0.9				0.4				0.01
Electrocardiogram	12	1.13 (1.04–1.22)	70.1		17	1.52 (1.35–1.70)	79.2		23	1.06 (1.04–1.08)	89.0	
Others	13	1.12 (1.05–1.19)	64.7		15	1.40 (1.25–1.56)	84.1		12	1.15 (1.10–1.20)	89.6	
Minimum of resting period				> 0.9				0.2				0.9
≥ 5 min	8	1.13 (0.99–1.29)	80.8		13	1.60 (1.38–1.85)	82.0		19	1.09 (1.06–1.12)	89.5	
< 5 min or unclear	17	1.11 (1.06–1.16)	54.7		19	1.39 (1.27–1.51)	75.5		16	1.10 (1.06–1.14)	94.5	
Posture				0.2				0.2				0.8
Supine	9	1.19 (1.06–1.35)	78.7		15	1.56 (1.32–1.84)	86.8		13	1.09 (1.05–1.13)	92.8	
Sitting/ recumbent/unclear	16	1.09 (1.04–1.14)	52.0		17	1.36 (1.26–1.47)	70.8		22	1.10 (1.07–1.12)	92.2	
Study quality*				0.05				0.01				0.4
7–9	16	1.08 (1.03–1.14)	66.8		18	1.33 (1.24–1.44)	73.2		28	1.09 (1.06–1.11)	91.3	
5–6	9	1.22 (1.14–1.31)	8.60		14	1.67 (1.45–1.92)	76.0		7	1.12 (1.05–1.20)	93.8	
Adjusted for ...												
Blood pressure				0.1				0.09				0.7
Yes	23	1.11 (1.06–1.16)	61.8		29	1.42 (1.32–1.53)	78.8		34	1.10 (1.07–1.12)	92.5	
No	2	1.22 (0.85–1.75)	61.0		3	1.97 (1.64–2.37)	13.6		1	1.07 (1.02–1.12)	–	
Smoking				–				0.7				0.8
Yes	25	1.12 (1.07–1.17)	66.7		31	1.45 (1.34–1.57)	81.9		32	1.09 (1.07–1.12)	92.2	
No	0	–	–		1	1.19 (0.45–3.18)	–		1	1.11 (1.08–1.14)	–	
Body mass index				0.6				0.8				0.2
Yes	19	1.13 (1.07–1.20)	65.5		25	1.44 (1.32–1.57)	78.6		29	1.09 (1.06–1.11)	92.2	
No	6	1.10 (1.09–1.20)	74.6		7	1.49 (1.22–1.82)	88.6		6	1.12 (1.08–1.15)	57.2	
Physical activity				0.5				0.3				0.3
Yes	13	1.15 (1.06–1.24)	70.9		17	1.52 (1.36–1.70)	76.8		14	1.08 (1.05–1.10)	93.4	
No	12	1.10 (1.03–1.17)	64.2		15	1.38 (1.23–1.55)	85.3		21	1.11 (1.07–1.16)	91.9	
Serum cholesterol/triglycerides				0.4				0.5				0.9
Yes	22	1.10 (1.06–1.15)	59.1		26	1.43 (1.33–1.54)	77.7		33	1.09 (1.07–1.11)	92.6	
No	3	1.21 (0.91–1.61)	87.1		6	1.50 (1.04–2.17)	88.5		2	1.10 (1.06–1.14)	18.5	
Diabetes/blood glucose				0.03				0.1				0.6
Yes	15	1.06 (1.02–1.11)	45.4		18	1.37 (1.25–1.50)	80.7		27	1.10 (1.07–1.13)	93.5	
No	10	1.21 (1.09–1.34)	65.5		14	1.58 (1.37–1.82)	78.7		8	1.08 (1.05–1.10)	75.4	
Alcohol				0.5				0.9				0.6
Yes	7	1.17 (1.04–1.31)	81.0		9	1.44 (1.30–1.59)	56.5		13	1.08 (1.04–1.13)	90.9	
No	18	1.10 (1.05–1.16)	58.1		23	1.45 (1.31–1.61)	85.1		22	1.10 (1.07–1.13)	93.2	
Education/socioeconomic status				0.3				0.4				0.3
Yes	10	1.16 (1.06–1.27)	57.8		10	1.37 (1.19–1.58)	76.3		10	1.07 (1.03–1.11)	87.4	
No	15	1.10 (1.04–1.15)	66.9		22	1.49 (1.36–1.64)	82.3		25	1.10 (1.08–1.13)	93.5	
No. covariates adjusted				0.8				0.7				0.1
≥ 6	10	1.13 (1.04–1.24)	72.3		13	1.43 (1.26–1.61)	80.7		17	1.07 (1.04–1.10)	88.9	
< 6	15	1.11 (1.05–1.18)	64.5		19	1.48 (1.33–1.64)	82.6		18	1.12 (1.08–1.15)	94.0	

Note: CI = confidence interval, CVD = cardiovascular disease, RR = relative risk.
 *Study quality was judged based on the Newcastle–Ottawa Scale (range 1–9 stars).

cohort studies included in the meta-analysis, 40 studies provided the results for all-cause mortality, involving 1 246 203 patients and 78 349 deaths, and 29 studies provided the results for cardiovascular mortality, involving 848 320 patients and 25 800 deaths. The follow-up duration ranged from 3 to 40 years. The study quality ranged from 5 to 9 stars (Appendix 2, www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.150535/-/DC1). Details about the included studies are shown in Table 1.

Quantitative synthesis

All-cause mortality

Pooled results on resting heart rate and risk of all-cause mortality are shown in Table 2. The

multivariate-adjusted relative risk of all-cause mortality with every 10 beats/min increment was 1.09 (95% CI 1.07–1.12) (Figure 1). Publication bias was detected ($p < 0.01$), and the corrected effect with the trim-and-fill method was 1.04 (95% CI 1.02–1.06). No individual study had an excessive influence to the pooled effect in sensitivity analysis. The relative risk of all-cause mortality was 1.12 (95% CI 1.07–1.17) for those with a resting heart rate of 60–80 beats/min and 1.45 (95% CI 1.34–1.57) for those with a resting heart rate greater than 80 beats/min.

Cardiovascular mortality

Pooled results on resting heart rate and risk of cardiovascular mortality are shown in Table 3. The relative risk of cardiovascular mortality with

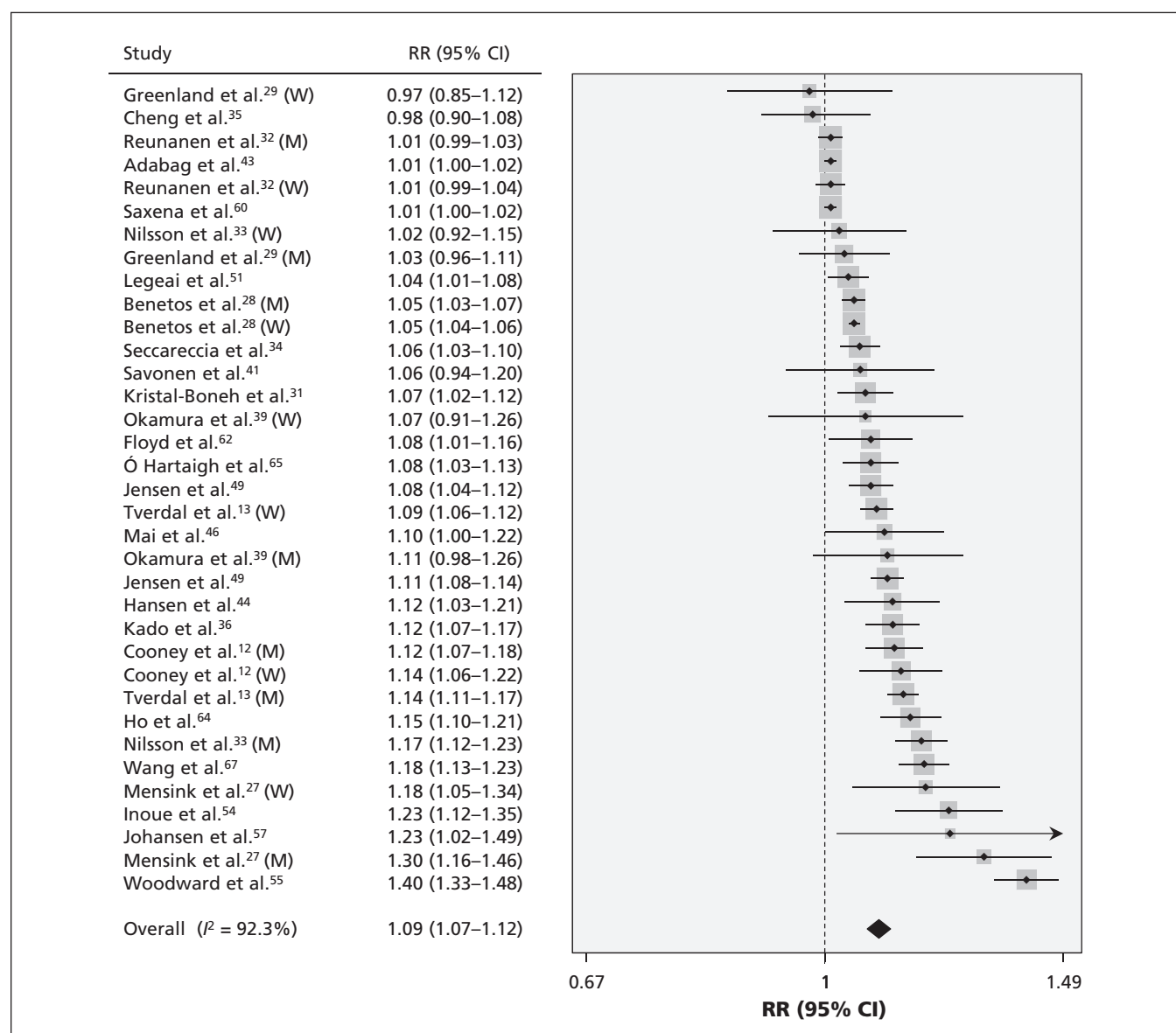


Figure 1: Risk of all-cause mortality for each 10 beats/min increase in resting heart rate. Note: CI = confidence interval, M = men, RR = relative risk, W = women.

Table 3: Pooled results on resting heart rate and risk of cardiovascular mortality

Variable	60–80 beats/min				> 80 beats/min				10 beats/min increment			
	No.	RR (95% CI)	<i>P</i> value, %	<i>p</i> value	No.	RR (95% CI)	<i>P</i> value, %	<i>p</i> value	No.	RR (95% CI)	<i>P</i> value, %	<i>p</i> value
Age-adjusted	13	1.24 (1.12–1.38)	39.8		13	1.70 (1.48–1.94)	40.2		26	1.42 (1.29–1.57)	56.9	
Multivariate-adjusted	19	1.08 (0.99–1.17)	55.8		22	1.33 (1.19–1.47)	61.0		32	1.08 (1.06–1.10)	81.0	
Excluding deaths during the first 1–5 yr									11	1.09 (1.05–1.12)	67.1	
Among those not taking heart rate–lowering medication									9	1.13 (1.07–1.19)	79.0	
Among studies adjusting for heart rate–lowering medication									7	1.15 (1.04–1.26)	88.0	
Follow-up duration, yr				0.6				0.1				0.08
> 10	12	1.06 (0.96–1.18)	60.4		15	1.26 (1.11–1.44)	68.3		26	1.06 (1.04–1.08)	75.4	
≤ 10	7	1.11 (0.96–1.29)	50.6		7	1.49 (1.34–1.65)	0.00		6	1.16 (1.05–1.28)	87.1	
Sample size				0.2				0.6				0.4
> 10 000	5	1.00 (0.88–1.14)	67.3		7	1.28 (1.04–1.57)	80.5		12	1.10 (1.06–1.14)	90.5	
≤ 10 000	14	1.12 (1.01–1.24)	47.6		15	1.35 (1.20–1.53)	39.6		20	1.06 (1.03–1.09)	59.3	
Mean age, yr				0.5				0.2				0.6
> 50	9	1.11 (0.99–1.24)	46.2		10	1.44 (1.31–1.57)	0.00		17	1.10 (1.05–1.14)	80.3	
≤ 50	10	1.05 (0.93–1.18)	64.4		12	1.25 (1.06–1.46)	73.3		15	1.07 (1.04–1.11)	82.7	
Region				0.5				0.6				0.05
Europe	10	1.10 (0.92–1.31)	72.1		12	1.28 (1.04–1.58)	75.9		18	1.07 (1.04–1.09)	77.3	
United States	4	1.03 (0.94–1.12)	0.00		6	1.42 (1.27–1.58)	0.00		7	1.05 (1.00–1.11)	70.8	
Asia	4	1.02 (0.88–1.19)	34.6		3	1.25 (1.02–1.52)	0.00		5	1.11 (1.02–1.21)	40.9	
Mixed	1	1.08 (0.99–1.18)	–		1	1.45 (1.28–1.64)	–		2	1.27 (1.00–1.60)	89.4	
Australia				0.2				0.3				0.1
Excluding CVD at baseline	14	1.04 (0.94–1.15)	59.9		14	1.26 (1.09–1.46)	66.3		21	1.06 (1.04–1.08)	78.3	
Yes	5	1.20 (1.02–1.41)	36.5		8	1.44 (1.26–1.64)	34.6		11	1.14 (1.06–1.21)	81.4	
No				0.2				0.6				0.4
Sex	9	1.15 (0.99–1.34)	67.3		11	1.44 (1.26–1.64)	50.1		14	1.08 (1.04–1.12)	73.1	
Male	5	0.98 (0.82–1.18)	42.1		6	1.04 (0.85–1.29)	57.4		9	1.03 (1.00–1.07)	26.2	
Female	5	1.04 (0.94–1.15)	35.3		5	1.46 (1.32–1.62)	0.00		9	1.12 (1.07–1.17)	92.0	
Both sexes				0.5				> 0.9				0.02
Resting heart rate assessment	10	1.10 (1.00–1.22)	27.5		10	1.32 (1.15–1.52)	42.2		19	1.05 (1.03–1.08)	75.5	
Electrocardiogram	9	1.04 (0.91–1.19)	71.6		12	1.33 (1.13–1.56)	71.2		13	1.14 (1.08–1.21)	86.2	
Others				0.6				0.2				0.7
Resting period	10	1.10 (0.97–1.24)	55.0		11	1.43 (1.29–1.58)	12.0		18	1.08 (1.04–1.11)	70.4	
≥ 5 min	9	1.05 (0.94–1.19)	61.3		11	1.23 (1.04–1.47)	74.4		14	1.09 (1.05–1.13)	87.6	
< 5 min or unclear				0.5				0.4				0.7
Posture	8	1.11 (0.95–1.30)	58.8		9	1.40 (1.24–1.59)	22.0		11	1.09 (1.04–1.13)	56.9	
Supine	11	1.05 (0.96–1.16)	55.0		13	1.28 (1.10–1.49)	71.8		21	1.07 (1.05–1.10)	81.7	
Sitting/ recumbent/unclear				0.2				0.05				0.1
Study quality*	13	1.04 (0.97–1.11)	26.5		15	1.24 (1.10–1.40)	61.6		27	1.06 (1.04–1.09)	76.0	
7–9	6	1.15 (0.89–1.47)	74.9		7	1.58 (1.37–1.83)	15.2		5	1.14 (1.03–1.26)	88.6	
5–6				0.1				0.4				0.7
Adjusted for ...				0.1				0.4				0.7
Blood pressure	17	1.06 (0.98–1.13)	40.8		18	1.29 (1.15–1.45)	59.1		31	1.08 (1.06–1.10)	81.6	
Yes	2	0.98 (0.36–2.67)	79.7		4	1.47 (1.10–1.98)	70.9		1	1.05 (0.98–1.12)	0.00	
No				–				–				0.7
Smoking	19	1.08 (0.99–1.17)	55.8		22	1.33 (1.19–1.47)	61.0		31	1.07 (1.05–1.10)	78.3	
Yes	–	–	–		–	–	–		1	1.12 (1.09–1.16)	0.00	
No				> 0.9				0.9				> 0.9
Body mass index	12	1.07 (0.98–1.18)	43.7		15	1.33 (1.20–1.48)	39.3		27	1.08 (1.05–1.10)	82.1	
Yes	7	1.07 (0.90–1.26)	71.5		7	1.32 (1.03–1.70)	80.2		5	1.08 (1.03–1.14)	57.0	
No				0.2				0.04				0.02
Physical activity	9	1.02 (0.91–1.14)	48.4		11	1.18 (0.99–1.41)	68.2		12	1.04 (1.02–1.06)	80.1	
Yes	10	1.13 (1.01–1.28)	58.7		11	1.46 (1.33–1.60)	17.1		20	1.13 (1.08–1.18)	70.1	
No				0.4				0.6				–
Serum cholesterol/triglycerides	17	1.06 (0.98–1.15)	41.9		18	1.30 (1.15–1.47)	58.9		32	1.08 (1.06–1.10)	81.0	
Yes	2	1.18 (0.74–1.88)	91.5		4	1.42 (1.11–1.81)	74.7		–	–	–	
No				0.3				0.3				0.7
Diabetes/blood glucose	12	1.04 (0.95–1.14)	48.4		13	1.26 (1.09–1.47)	67.9		25	1.09 (1.06–1.12)	83.4	
Yes	7	1.14 (0.96–1.35)	63.9		9	1.43 (1.23–1.66)	44.9		7	1.06 (1.02–1.10)	66.9	
No				0.8				0.6				0.7
Alcohol	3	1.02 (0.93–1.12)	0.00		6	1.40 (1.21–1.61)	22.0		11	1.07 (1.04–1.10)	79.1	
Yes	16	1.08 (0.98–1.19)	61.0		16	1.30 (1.13–1.49)	67.8		21	1.09 (1.05–1.13)	82.2	
No				0.6				0.3				0.1
Education/socioeconomic status	6	1.04 (0.93–1.17)	6.70		8	1.24 (1.10–1.39)	38.3		10	1.04 (1.02–1.07)	71.9	
Yes	13	1.09 (0.98–1.21)	65.8		14	1.41 (1.20–1.66)	66.4		22	1.11 (1.07–1.15)	82.8	
No				0.9				0.6				0.1
No. covariates adjusted												
≥ 6	5	1.05 (0.97–1.14)	0.00		6	1.26 (1.04–1.53)	45.9		17	1.05 (1.03–1.07)	75.8	
< 6	14	1.07 (0.95–1.20)	65.5		16	1.35 (1.19–1.53)	65.6		15	1.17 (1.07–1.17)	78.5	

Note: CI = confidence interval, CVD = cardiovascular disease, RR = relative risk.

*Study quality was judged based on the Newcastle–Ottawa Scale (range 1–9 stars).

every 10 beats/min increment was 1.08 (95% CI 1.06–1.10) (Figure 2). Publication bias was detected ($p < 0.01$), and the corrected effect with the trim-and-fill method was 1.03 (95% CI 1.01–1.06). No individual study had an excessive influence to the pooled effect in sensitivity analysis. The relative risk of cardiovascular mortality was 1.08 (95% CI 0.99–1.17) for those with a resting heart rate of 60–80 beats/min and 1.33 (95% CI 1.19–1.47) for those with a rate of greater than 80 beats/min.

Subgroup analysis and meta-regression

As shown in Tables 2 and 3, between-study heterogeneity was found. Overall, no single factor successfully explained the between-study heterogeneity; however, when all of the factors were included in meta-regression simultaneously, they explained all (100%), most (89.2%, 61.9%) or part (44.9%, 37.6%) of the heterogeneity (Appendix 3, www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.150535/-DC1).

To examine potential influencers (e.g., medication and disease states) of resting heart rate, we conducted several subgroup analyses. Among patients not taking heart rate-lowering medication, the relative risk of all-cause and cardiovascular mortality was 1.11 (95% CI 1.06–1.16) and 1.13 (95% CI 1.07–1.19), respectively, with each 10 beats/min increment. To take into account the possibility of an effect by an existing or preclinical disease at baseline, we conducted a separate analysis in which deaths within the first 6 months to 5 years of follow-up were excluded, and the risk of all-cause mortality and cardiovascular mortality with each 10 beats/min increment was 1.09 (95% CI 1.06–1.13) and 1.09 (95% CI 1.05–1.12), respectively. For studies excluding patients with cardiovascular disease at baseline, the relative risk of all-cause mortality and cardiovascular mortality with each 10 beats/min increment was 1.09 (95% CI 1.06–1.12) and 1.06 (95% CI 1.04–1.08), respectively.

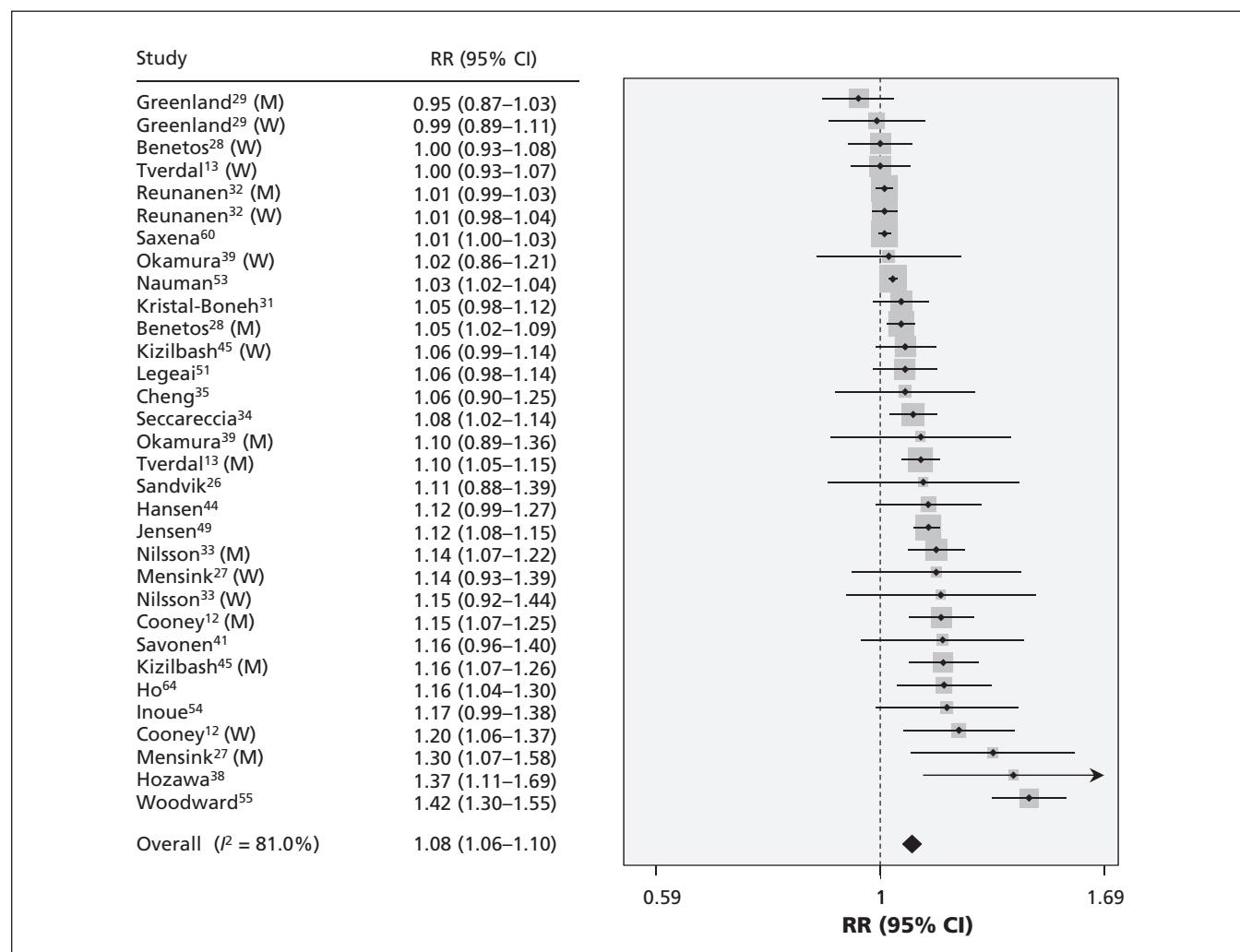


Figure 2: Risk of cardiovascular mortality for each 10 beats/min increase in resting heart rate. Note: CI = confidence interval, M = men, RR = relative risk, W = women.

Dose–response analysis with restricted cubic spline functions

For all-cause mortality, data from 13 studies including 26 636 deaths were used. The departure from a linear relation was not significant ($p_{\text{for nonlinearity}} = 0.1$). Compared with 45 beats/min, the risk of all-cause mortality increased significantly with increasing levels of resting heart rate (Figure 3A).

For cardiovascular mortality, data from 10 studies including 6502 deaths were used.

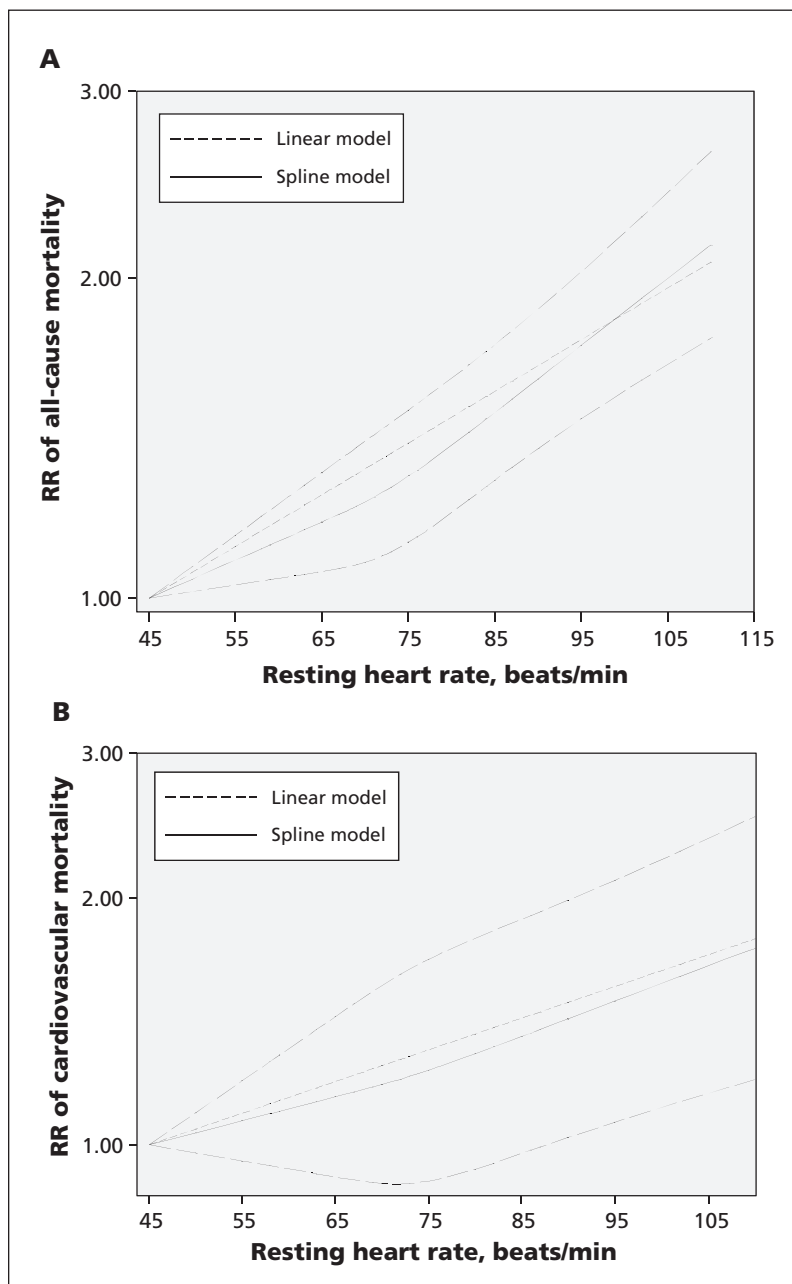


Figure 3: The dose–response analysis of resting heart rate with risk of (A) all-cause mortality and (B) cardiovascular mortality. The solid and long dash lines represent the estimated relative risks (RRs) and 95% confidence intervals. The short dash lines represent the linear relation.

The departure from a linear relation was not significant ($p_{\text{for nonlinearity}} = 0.6$). Compared with 45 beats/min, the risk of cardiovascular mortality increased significantly at 90 beats/min (Figure 3B).

With use of 70 beats/min as the reference, the linear dose–response analysis indicated a protective effect of lower resting heart rate (45–69 beats/min) on risk of all-cause and cardiovascular mortality, respectively (Appendix 4, www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.150535/-/DC1).

Interpretation

Results from this meta-analysis suggest the risk of all-cause and cardiovascular mortality increased by 9% and 8% for every 10 beats/min increment of resting heart rate. Compared with 45 beats/min, the risk of all-cause mortality increased significantly with increasing resting heart rate in a linear relation, but a significantly increased risk of cardiovascular mortality was observed at 90 beats/min. The threshold (90 beats/min) associated with cardiovascular mortality is consistent with the traditionally defined tachycardia threshold of 90 or 100 beats/min for prevention of cardiovascular disease.⁵

One mechanism is that higher resting heart rate is a marker of an imbalance between the vagal and the sympathetic tone, and dysfunctional autonomic nervous activity likely plays a central role in the pathogenesis of numerous adverse health conditions.^{5,68} A relatively high heart rate has direct detrimental effects on progression of coronary atherosclerosis, on occurrence of myocardial ischemia and ventricular arrhythmias, and on left ventricular function. In this meta-analysis, the magnitude of association between resting heart rate and all-cause mortality was stronger than that with cardiovascular mortality, and this discrepancy can be expected because resting heart rate has also been found to be associated with noncardiovascular mortality.^{28,34,44,51,54,69}

One main concern lies in whether a high resting heart rate is an independent predictor, because higher heart rates coexist with traditional risk factors of cardiovascular disease and poor health status.^{10–13,70} Overall, the association of resting heart rate with risk of all-cause and cardiovascular mortality is independent of traditional risk factors of cardiovascular disease, suggesting that resting heart rate is a predictor of mortality in the general population. In addition, previous studies found that resting heart rate is also related to prognosis in settings of substantial cardiovascular comorbidities, such as renal disease, erectile dysfunction and pulmonary hypertension, as well as in noncardiovascular conditions such as chronic obstructive pulmonary disease.⁷¹ To comply with

the definition of a risk factor, a reduction in heart rate by therapy should be associated with improved clinical outcomes. Several trials with ivabradine (the specific heart rate-reducing agent without any other known cardiovascular effects) have been conducted to explore this issue. Although no benefit was observed of heart rate reduction on outcomes in patients with stable coronary artery disease without clinical heart failure and with a heart rate of 70 beats/min or greater,⁷² a higher heart rate may serve as a risk factor for cardiovascular mortality and all-cause mortality in patients with left-ventricular systolic dysfunction with coronary artery disease and/or heart failure^{73,74} (Appendix 5, www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.150535/-/DC1). These findings suggest that the association of heart rate reduction with outcomes may differ among populations of different risk, and higher heart rate is due to different pathophysiological mechanisms in different conditions.⁵

A linear relation was found between resting heart rate and risk of all-cause mortality and cardiovascular mortality, respectively. Among the included studies, only 3 studies described the dose-response relation continuously,^{13,34,64} and all indicated a linear relation. However, a J-shaped curve was also indicated by categorizing resting heart rate.^{44,48,55} Because this is a meta-analysis focusing on the general population (i.e., excluding studies in disease-specific populations), patients with a very low resting heart rate are likely to be more physically fit. Therefore, more benefit could be anticipated for patients with a very low resting heart rate. In addition, findings from trials involving patients with cardiovascular disease also indicated the possibility of “the slower the heart rate, the better.”⁷⁵

Limitations

Our study had several limitations. First, measurement of resting heart rate is susceptible to numerous factors,⁷⁶ and nighttime heart rate was found to be a better prognostic variable relative to resting heart rate and 24-hour heart rate; nighttime heart rate should be a better measure of heart rate because both the interference of sensory input as well as physical and mental activities were minimized.⁵⁷ Second, patients with cardiovascular disease or subclinical cardiovascular disease with no antihypertensive treatment at baseline could have started taking heart rate-lowering medications during follow-up, and this would lead to an underestimation of the true magnitude of the observed associations. Third, although we extracted risks that reflected the greatest degree of control for potential confounders, the covariates adjusted and the extent to which they were adjusted varied

in the original studies. Fourth, single factor did not successfully explain the substantial between-study heterogeneity; however, meta-regression suggested that population characteristics and study designs might contribute in concrete to the heterogeneity. Finally, we searched for only English- and Chinese-language studies, and we found publication bias. However, the observed associations remained after incorporating theoretical missing studies.

Conclusion

Resting heart rate was associated with risk of all-cause and cardiovascular mortality in the general population, independent of traditional cardiovascular risk factors. However, considering that the covariates adjusted for and the extent to which they were adjusted for varied in the included studies, as well as the presence of between-study heterogeneity and publication bias, collaborative pooling of individual participant data from prospective cohort studies is needed to better describe the association. Identification of the contribution of heart rate reduction on effects of cardiovascular events and mortality by other interventions like exercise with a clinical trial in the general population will provide evidence on whether heart rate is also a risk factor. Further studies are warranted to develop a prediction algorithm that would consider both resting heart rate and classic cardiovascular risk factors to allow physicians to use resting heart rate in clinical settings.

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