




ORIGINAL RESEARCH

Childhood Bradycardia Associates With Atrioventricular Conduction Defects in Older Age: A Longitudinal Birth Cohort Study

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BACKGROUND: This study explored the association between childhood bradycardia and later-life cardiac phenotype using longitudinal data from the 1946 National Survey of Health and Development (NSHD) birth cohort.

METHODS AND RESULTS: Resting heart rate was recorded at 6 and 7 years of age to provide the bradycardia exposure defined as a childhood resting heart rate <75 bpm. Three outcomes were studied: (1) echocardiographic data at 60 to 64 years of age, consisting of ejection fraction, left ventricular mass index, myocardial contraction fraction index, and E/e'; (2) electrocardiographic evidence of atrioventricular or ventricular conduction defects by 60 to 64 years of age; and (3) all-cause and cardiovascular mortality. Generalized linear models or Cox regression models were used, and adjustment was made for relevant demographic and health-related covariates, and for multiple testing. Mixed generalized linear models and fractional polynomials were used as sensitivity analyses. One in 3 older adults with atrioventricular conduction defects had been bradycardic in childhood, with defects being serious (Mobitz type II second-degree atrioventricular block or higher) in 12%. In fully adjusted models, childhood bradycardia was associated with 2.91 higher odds of atrioventricular conduction defects (95% CI, 1.59–5.31; $P=0.0005$). Associations persisted in random coefficients mixed generalized linear models (odds ratio, 2.50; 95% CI, 1.01–4.31). Fractional polynomials confirmed a linear association between the log odds of atrioventricular conduction defects at 60 to 64 years of age and resting heart rate at 7 years of age. There was no association between bradycardia in childhood and mortality outcomes or with echocardiographic parameters and ventricular conduction defects in older age.

CONCLUSIONS: Longitudinal birth cohort data indicate that childhood bradycardia trebles the odds of having atrioventricular conduction defects in older age, 88% of which are benign. In addition, it does not influence mortality or heart size and function. Future research should concentrate on identifying children at risk.

Key Words: atrioventricular conduction defects ■ cardiovascular disease ■ childhood bradycardia

A high resting heart rate (RHR) in older age has been previously associated with cardiovascular morbidity and mortality in both healthy individuals¹ and special populations.² On the one hand, a low RHR (bradycardia per se) has been associated with cardiovascular fitness (due to increased vagal tone in the physically active), but on the other hand, it can be a harbinger of genuine conduction system disease. Some studies found that asymptomatic adult

bradycardia was associated with a modest reduction in cardiovascular mortality,³ but others found no association.⁴

Fewer studies have focused on the prognostic relevance of RHR in childhood, which is therefore still a matter of debate in the scientific community. A high RHR at 11 years of age has been previously weakly associated with all-cause mortality in the NSHD (National Survey of Health and Development) cohort.⁵

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CLINICAL PERSPECTIVE

What Is New?

- A high resting heart rate in childhood has been linked with cardiovascular morbidity and mortality, whereas neonatal bradycardia has been linked to premature mortality. Little is known about the long-term effects of childhood bradycardia on cardiovascular disease.
- Our longitudinal birth cohort study shows that childhood bradycardia approximately triples the odds of having atrioventricular conduction defects in older age. Twelve percent were severe forms of atrioventricular block requiring a permanent pacemaker. However, childhood bradycardia does not influence mortality or heart size and function in later life.

What Are the Clinical Implications?

- Future research should investigate genetic and life-course risk factors that contribute to the development of higher-order atrioventricular conduction block in children with bradycardia.
- It is also clinically relevant to establish whether later-life exposure to atrioventricular blocking drugs (eg, β -blockers) could accelerate the progression of atrioventricular dysfunction in those with known childhood bradycardia.

Nonstandard Abbreviations and Acronyms

FP	fractional polynomial
LVmass_i	left ventricular mass index
MCF_i	myocardial contraction fraction index
NSHD	National Survey of Health and Development
RHR	resting heart rate
SEP	socioeconomic position

In addition, neonatal bradycardia has been shown to be associated with premature pediatric mortality.⁶ However, little is known about the long-term effects of childhood bradycardia in terms of other markers of cardiovascular disease.

To understand the cardiovascular implications of childhood bradycardia, we analyzed life-course data in participants from the 1946 Medical Research Council (MRC) NSHD cohort. We focused on the association of childhood bradycardia with cardiac size, function, and conduction system disease in older age, and with all-cause and cardiovascular mortality.

METHODS

Study Population

Participants were from the MRC NSHD, a birth cohort study including 5362 individuals (2547 men and 2815 women) born in 1 week in March 1946 in Britain. The cohort has been extensively followed up with periodic anthropometric, socioeconomic, lifestyle, and health assessments that have been described elsewhere.⁷

Ethical Approval

The 2006 to 2010 NSHD data collection sweep included an in-depth cardiovascular assessment and was granted ethical approval from the Greater Manchester Local Research Ethics Committee and the Scotland Research Ethics Committee,⁷ and written informed consent was given by all study participants. Our project was approved by the NSHD Committee. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Data Availability

NSHD data are available from: <https://www.nshd.mrc.ac.uk/data>.

Outcomes

Between 2006 and 2010, when study members were 60 to 64 years old, NSHD participants residing in the United Kingdom who had not been lost to follow-up or withdrawn, were invited to attend a clinic-based assessment. Twelve-lead resting surface electrocardiography was performed, interpreted, and recorded according to the Minnesota classification.⁸ In our study, atrioventricular conduction defects were coded as 1 for the presence of any of the following Minnesota categories: 6-1, 6-2-1, 6-2-2, 6-2-3, 6-3, 6-8, 8-5-1, 8-5-2, 8-6-1, 8-6-2, 8-6-3, and 8-6-4 or 0 otherwise. Ventricular conduction defects were defined as 1 for the presence of any Minnesota group 7 subcategory or 0 otherwise. Thus, our electrocardiography outcomes (both binary variables) were atrioventricular or ventricular conduction defects.

During the same 2006 to 2010 clinic visit, resting transthoracic echocardiography was performed by an experienced cardiologist and 2 radiographers (intra-class correlation coefficients >0.80⁹) using General Electric Vivid I machines. Left ventricular ejection fraction (EF) was calculated by the biplane Simpson method. Left ventricular mass was indexed to height^{1.7} to obtain the left ventricular mass index (LVmass_i).¹⁰ Although body surface area is often used in clinical

practice for indexation, it creates a bias for individuals who are overweight. Myocardial contraction fraction index (MCF_i) was calculated as the ratio between stroke volume and myocardial volume. Myocardial volume was calculated by dividing LVmass_i by mean myocardial density (1.04 g/mL).¹¹ E/e' was calculated by dividing peak mitral valve velocity (E) by the average of lateral and septal mitral annular early diastolic velocity (e').¹² Left ventricular end-diastolic volume index (LVEDV_i) was derived by dividing left ventricular end-diastolic volume by height^{1.7}.¹⁰ Thus, our echocardiographic outcomes (all continuous variables) were EF, LVmass_i, MCF_i, E/e', and LVEDV_i.

Our mortality outcomes were all-cause mortality and cardiovascular mortality starting at 7 years of age out to 73 years of age. Prior to 1971, only all-cause mortality data were available for NSHD study members, because they only started to be flagged for death notification on the National Health Service Central Register in 1971. Since then, NSHD received from the National Health Service Central Register an automatic notification of death including the date and the cause. Therefore, for the cardiovascular mortality analyses, only individuals who were flagged for death by the National Health Service Central Register (4638) were considered to capture the reliable cause of death.

Exposures: RHR

RHR in childhood was recorded at 6 and 7 years of age in a seated position at the radial artery at the end of a medical school examination. Bradycardia in childhood was defined as a RHR <75 bpm corresponding to the 10th centile¹³ at either 6 or 7 years of age or both.

Covariates

Male or female sex was assigned at birth. In the same visit, where the RHR was assessed, the child's height and weight were also measured. Thus, body mass index (BMI) was derived as weight/height² at 6 and 7 years of age. Participants' childhood socioeconomic position (SEP) was evaluated based on the father's occupation and classified according to the UK Office of Population Censuses and Surveys Registrar General's social class (professional, intermediate, skilled non-manual, skilled manual, partly skilled, and nonskilled). Lastly, the presence of congenital heart disease (discovered until 1961) was also available and recorded as yes/1 or no/0. No further entries on congenital heart disease were made in the NSHD database after 1961.

Statistical Analysis

Statistical analysis was performed in R (version-3.6.3; R Foundation for Statistical Computing, Vienna, Austria). Distribution of data was assessed on histograms, and normality checks were assessed by the Shapiro-Wilk

test. Continuous variables are expressed as mean±1 SD or median (interquartile range) as appropriate; categorical variables are expressed as count and percent. A *P* value <0.05 was considered significant.

Regression models were developed using RHRs at 6 and 7 years of age as exposures to predict echocardiographic (EF, LVmass_i, MCF_i, E/e', and left ventricular end-diastolic volume index), electrocardiography (atrioventricular or ventricular conduction defect), and mortality (all-cause and cardiovascular mortality) outcomes. As a result of the skewed distribution of echocardiographic parameters, generalized linear models with gamma distribution and log link were used for all echocardiographic regression analyses. As the echocardiographic variables were binary, generalized linear models with binomial distribution and logit link (equivalent to logistic regression) were used. Lastly, Cox proportional hazard regression models were employed to investigate the associations between RHR and mortality outcomes after removing the participants who died before 7 years of age (the start of follow-up). Childhood regression analyses were each adjusted for sex, childhood SEP, BMI at 6 and 7 years of age (except in cases where the outcome variable was already indexed to height), and for the presence of congenital heart disease.

To maintain the sample size and minimize data missingness bias, we used multiple imputation to generate missing covariates. Data missingness for each covariate per exposure–outcome pair is presented in Table S1. The imputation model included all the variables from all the fully adjusted analytic models, namely all exposures (RHR at 6 and 7 years of age), all outcomes (ie, electrocardiographic, echocardiographic, and mortality outcomes) and all covariates (childhood SEP, BMI at 6 and 7 years, and the presence of congenital heart disease). We used predictive mean matching multiple imputation to generate 50 sets of covariates using chained equations. Regression coefficient estimates and their associated variance metrics were calculated for each of the 50 data sets and combined using the Rubin rule. Then, we filtered significant results correcting for multiple testing at a false discovery rate of 0.05.

Lastly, we ran sensitivity analyses as follows: (1) We performed a complete case analysis. (2) We used a cutoff of ≤70 bpm to define bradycardia in men, as per the United States National Health Statistics Report from 2011 (<https://www.cdc.gov/nchs/data/nhsr/nhsr041.pdf>). (3) To account for within-subject correlated repeated measures at 6 and 7 years of age (namely RHR and BMI), we used random coefficients generalized linear mixed models to test the associations between childhood bradycardia and our outcomes. In these analyses, the RHR and BMI at 6 and 7 years of age were used as separate measures in which random

effects per participant due to their repeated nature were considered. (4) We selected the best-fitting function using fractional polynomials (FPs) to account for any nonlinear and asymmetric relationships between RHR at 6 and 7 years of age as a continuous and in our outcomes. To allow for flexibility in fitting a curve with a single turning point, we considered the best-fitting multivariable second-degree FP of RHR. We used a closed-test procedure with backward elimination¹⁴ and power transformations from the set $-2, -1, -0.5, 0, 0.5, 1, 2, 3$, where 0 was the log transformation, for our exposures (RHR at 6 years of age and RHR at 7 years of age as separate continuous variables) and covariates (sex, childhood SEP, BMI at 6 years of age, BMI at 7 years of age, and the presence of congenital heart disease). For the best power transformation selection, we used a deviance difference test with 4 degrees of freedom, where the best-fitting first-degree/second-degree FP was compared sequentially against null, the linear model, and the first-degree/second-degree FP (as appropriate). The purpose of this analysis was to

model each outcome as a sum of the FP of RHR and relevant covariates.

RESULTS

Participant Characteristics

Participant characteristics are summarized in Table 1. Heart rate data were available for 4210 participants at 6 years and for 4114 participants at 7 years. Of the 2856 participants invited to attend the clinic visit at 60 to 64 years of age, 1690 attended and 1653 had echocardiography, of which 1617 had acceptable image quality. In addition, a contemporaneous ECG was available for 1631 participants. Lastly, 711 participants died between 1953 and 2019. Between 1971 and 2019, 181 participants had a cardiovascular-related death. Thus, the number of participants included was 4381 for mortality, 1631 for electrocardiography, and 1617 for the echocardiography analyses. A study flowchart is provided in Figure 1.

Table 1. Participant Characteristics

	Overall		Men		Women	
	No.	Result	No.	Result	No.	Results
Childhood, 6–7 y	4441	686 (15.5%)	2320	393 (16.9%)	2121	293 (12.6%)
Bradycardia (RHR <75 bpm) at either age 6 or 7 y, %	4210	329 (7.7%)	2189	165 (7.5%)	2021	164 (8.1%)
Childhood socioeconomic position, % nonmanual*	4147	2438 (58.8%)	2175	1255 (57.7%)	1972	1203 (61.0%)
Body mass index at age 6 y, kg/m ²	3821	15.81 (1.38)	2033	14.93 (1.38)	1788	15.61 (1.37)
Body mass index at age 7 y, kg/m ²	3891	15.81 (1.47)	2035	15.61 (1.50)	1856	15.78 (1.43)
Congenital heart disease, %	4235	22 (0.5%)	2221	12 (0.5%)	2014	10 (0.5%)
Age 60–64 y						
Ejection fraction, %	1315	64.90 (59.88–69.25)	693	64.89 (59.83–69.13)	622	64.93 (60.09–69.39)
Left ventricular mass index, g/m ²	1648	99.58 (75.61–363.37)	794	114.56 (86.03–367.96)	854	86.37 (68.27–167.79)
Myocardial contraction fraction index	1366	0.52 (0.22–0.72)	674	0.53 (0.21–0.76)	692	0.51 (0.24–0.70)
Left ventricular end diastolic volume index	1320	46.55 (40.68–54.32)	699	46.78 (40.81–54.76)	621	46.19 (40.48–53.75)
E/e'	1368	7.63 (6.46–9.16)	724	7.74 (6.57–9.28)	644	7.50 (6.32–8.99)
Atrioventricular conduction defects, % [†]	1480	52 (3.5%)	786	29 (3.7%)	694	23 (3.3%)
Permanent pacemaker, % [‡]	1480	5 (0.3%)	786	4 (0.5%)	694	1 (0.1%)
Ventricular conduction defects, % [†]	1480	480 (32.4%)	786	241 (30.7%)	694	239 (34.4%)
Age 73 y						
All-cause mortality, %	4381	711 (16.2%)	2281	412 (18.1%)	2100	299 (14.2%)
Cardiovascular mortality, %	4370	181 (4.1%)	2273	113 (5.0%)	2097	68 (3.2%)

Only participants who had at least 1 outcome and at least 1 exposure are presented. Results are reported as counts (%), mean (SD), or median (interquartile range). RHR indicates resting heart rate.

*Defined as socioeconomic position classes IIIIM to V.

[†]Defined according to the Minnesota classification.

[‡]Considering only participants with permanent pacemaker as opposed to other cardiac implantable electronic devices (such as implantable cardiac defibrillators and resynchronization devices).

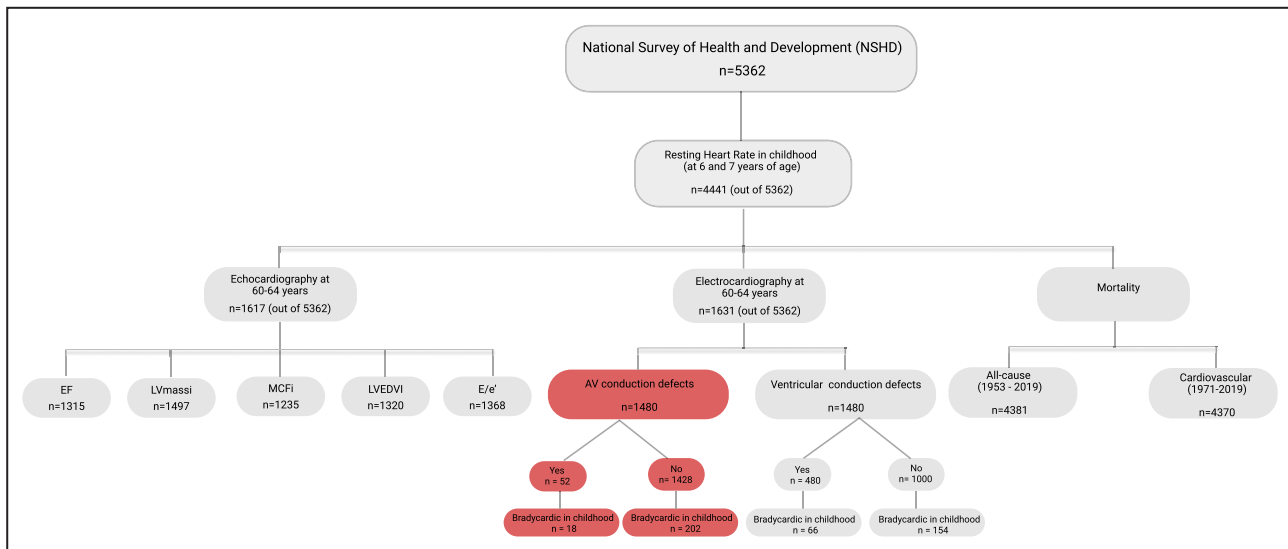


Figure 1. Flowchart of the study design.

The National Survey of Health and Development (NSHD) consists of 5362 individuals recruited in 1 week in March 1946 in Britain. Our exposure was resting heart rate (RHR) at 6 or 7 years of age, which was available for 4441 out of the 5362 participants. Our outcomes were derived from electrocardiography data at 60 to 64 years of age (available for 1631 out of 5362 participants), echocardiography data (acceptable image quality echocardiogram available for 1617 out of 5362), and mortality data (all-cause mortality available from 1946 and cardiovascular mortality available from 1971, when the study members started to be flagged for death notification on the National Health Service Central Register [NHSCR]). The number of participants for which we had both the exposure and outcome data is presented underneath each specific outcome variable (bottom row) in the figure. Atrioventricular (AV) conduction defects (red) emerged as significant outcomes in the statistical analysis. EF indicates ejection fraction; LVEDV_i, left ventricular end-diastolic volume indexed to height^{1,7}; LVmass_i, left ventricular mass indexed to height^{1,7}; and MCF_i, myocardial contraction fraction indexed to height^{1,7}.

Bradycardia in Childhood

Bradycardia was associated with male sex ($P < 0.0001$) and a higher BMI in childhood ($P = 0.009$), but it was not associated with childhood socioeconomic position ($P = 0.789$). A total of 52 individuals exhibited atrioventricular conduction defects at 60 to 64 years of age, of whom 46 (88.46%) had benign atrioventricular blocks (first-degree atrioventricular block, Mobitz I second-degree atrioventricular block) and 6 had more serious atrioventricular blocks (Mobitz II second-degree atrioventricular block or higher). Of the 52 individuals with atrioventricular conduction defects at 60 to 64 years of age, 18 (34.5%) had a RHR < 75 bpm at either 6 or 7 years of age. Conversely, of the 220 bradycardic individuals in childhood, 18 (8.2%) ended up developing atrioventricular conduction defects by 60 to 64 years of age. Bradycardia in childhood was associated with 2.93 higher odds (95% CI, 1.62–5.32) of atrioventricular conduction defects at 60 to 64 years of age after adjusting for sex ($n = 1480$, $P < 0.0001$, Table 2). Even after adjusting for sex, childhood SEP, BMI at 6 years of age, BMI at 7 years of age, and for the presence of congenital heart disease, the association persisted (odds ratio [OR], 2.91; 95% CI, 1.59–5.31). The association between childhood bradycardia and atrioventricular conduction defects in the fully adjusted remained significant at a false

discovery rate of 0.05. However, there was no association between childhood bradycardia and Mobitz II second-degree or higher atrioventricular block (OR, 1.07; 95% CI, 0.12–9.36; $P = 0.951$). An alluvial plot for the association between childhood bradycardia and later-life atrioventricular conduction defects is presented in Figure 2.

There was no association between bradycardia in childhood and ventricular conduction defects or echocardiographic parameters (EF, LVmass_i, MCF_i, left ventricular end-diastolic volume index, and E/e') or mortality outcomes.

Sensitivity Analyses

In the complete case analysis, all significant associations persisted (Table S2). The associations between childhood bradycardia defined as an RHR of ≤ 70 bpm and atrioventricular conduction defects persisted in male subjects in fully adjusted models (OR, 2.25; 95% CI, 1.15–7.46; $P = 0.025$). Here, covariates were generated using multiple imputation as in the main analysis.

In the random coefficients generalized linear mixed models (Table S3), associations between childhood bradycardia and atrioventricular conduction defects persisted in the fully adjusted model (OR, 2.50; 95% CI, 1.01–4.31; $P = 0.047$).

Table 2. Associations Between Childhood Bradycardia and Echocardiographic (EF, LVmass, MCF_i, LVEDV_i and E/e'), Electrocardiographic (AV or Ventricular Conduction Defect), and Mortality (All-Cause and Cardiovascular) Outcomes

Outcome	No.	Model I*		Model II†	
		Exponentiated β (95% CI)	P value	Exponentiated β (95% CI)	P value
EF	1315	0.99 (0.97–1.01)	0.217	0.99 (0.97–1.01)	0.232
LVmass _i	1497	1.03 (0.91–1.16)	0.635	1.03 (0.92–1.16)	0.575
MCF _i	1235	0.94 (0.86–1.04)	0.224	0.94 (0.85–1.03)	0.188
LVEDV _i	1320	1.02 (0.99–1.06)	0.233	1.02 (0.99–1.06)	0.203
E/e'	1368	1.00 (0.96–1.04)	0.789	0.99 (0.96–1.03)	0.796
		Odds ratio (95% CI)		Odds ratio (95% CI)	
AV conduction defects	1480	2.93 (1.62–5.32)	<0.0001 [‡]	2.91 (1.59–5.31)	0.0005 [‡]
Ventricular conduction defects	1480	0.81 (0.59–1.12)	0.194	0.81 (0.59–1.11)	0.187
		Hazard ratio (95% CI)		Hazard ratio (95% CI)	
All-cause mortality	4381	0.96 (0.78–1.18)	0.680	0.93 (0.76–1.14)	0.490
Cardiovascular mortality	4370	1.16 (0.79–1.71)	0.446	1.09 (0.74–1.61)	0.652

All reported analyses here consisted of generalized linear models with gamma distribution and log link for EF, LVmass_i, MCF_i, LVEDV_i, and E/e', generalized linear models with binomial distribution and logit link for AV or ventricular conduction defect, and Cox proportional hazard regression models for all-cause and cardiovascular mortality outcomes. AV indicates atrioventricular; EF, ejection fraction; LVEDV_i, left ventricular end-diastolic volume indexed to height^{1,7}; LVmass_i, left ventricular mass indexed to height^{1,7}; and MCF_i, myocardial contraction fraction indexed to height^{1,7}.

*Model I was adjusted for sex.

†Model II was adjusted for sex, childhood socioeconomic position, body mass index at 6 and 7 years of age, and for the presence of congenital heart disease for all except the indexed variables (LVmass_i, MCF_i, and LVEDV_i) where adjustment was made for height instead of body mass index.

[‡]Significant P values filtered at a false discovery rate of 0.05.

The best-fitting FPs for each outcome are presented in Table S4. The log odds of atrioventricular conduction defects at 60 to 64 years of age were linearly associated with RHR at 7 years of age using the formula

$$4.37 - (4.85 \times RHR)/100$$

(Figure S1), but RHR at 6 years of age did not make an FP or a sum of FPs best fit with the outcome of atrioventricular conduction defects. Thus, individuals with a RHR lower than 90 bpm at 7 years of age had higher odds of atrioventricular conduction defects, suggesting that the effects may extend beyond the 10th percentile cutoff for RHR (ie, 75 bpm) used in the main analyses.

DISCUSSION

Using longitudinal data from the NSHD British birth cohort, the world's longest-running birth cohort with continuous follow-up, we show that bradycardia in childhood could be relevant to cardiac health in older age. Childhood bradycardia was associated with having atrioventricular conduction defects by the seventh decade. On the other hand, having a low RHR in childhood was not associated with mortality or with heart

size and function parameters by echocardiography in older age.

RHR plays a pivotal role in pediatric clinical practice, and because of its prognostic importance it is incorporated into many scoring systems. Given the known anatomical and physiological cardiovascular changes that occur with age, age-specific cutoffs for defining bradycardia are commonly used.¹³ In clinically stable asymptomatic children, bradycardia is frequently seen as a marker of autonomic dysregulation dominated by vagal hyperactivity.⁶ Traditionally, a low RHR has been perceived as beneficial, because it is thought to improve diastolic myocardial perfusion and promote angiogenesis.¹⁵ However, our data suggest that childhood bradycardia could be an early marker of future atrioventricular dysfunction. Over a third of those with atrioventricular conduction defects by the seventh decade of life were bradycardic in childhood in this study.

One hypothesis is that childhood bradycardia is a surrogate of an underlying dysfunctional cardiac conduction system established before birth. The morphogenesis of the cardiac conduction system is yet to be fully elucidated, because complex interactions exist between multiple regulatory genes.¹⁶ Speculatively, the specific location of the pathology could be either in the sinoatrial or atrioventricular node, or it could be intra-atrial, intra-Hisian, or infra-Hisian. Our study is missing

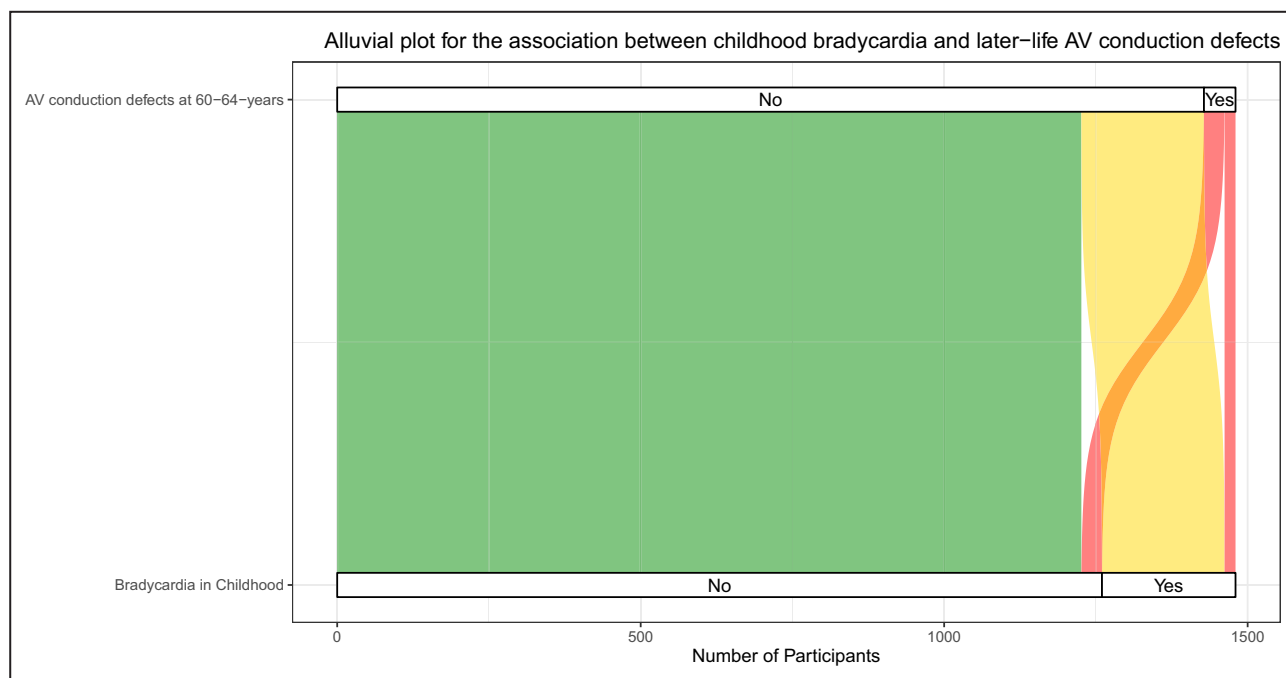


Figure 2. Alluvial plot for the association between childhood bradycardia and later-life atrioventricular (AV) conduction defects.

Study participants were split according to whether they expressed the adverse phenotype of AV conduction defects. Participants are color coded as follows: green=those who were never bradycardic and did not have ECG evidence of AV conduction defects at 60–64 years of age, yellow=those who were bradycardic in childhood but did not develop AV conduction defects in older age, red=those who developed AV conduction defects at 60–64 years regardless of whether they were bradycardic or not at 6 or 7 years of age.

the electrophysiological data needed to elucidate this matter. If a vulnerable atrioventricular node is found to be the culprit, future research will need to examine whether subsequent exposure to negatively chronotropic drugs, such as β -blockers, in any way accelerates the progression of cardiac conduction system disease in those with a history of childhood bradycardia. This is especially relevant, because the current evidence suggests that specialized conduction cells might suffer functional alterations throughout life.¹⁷

In adulthood, bradycardia (homogeneously defined as <60 bpm) can be both a positive (eg, increased vagal tone in athletes) or negative (eg, underlying conduction system disease) health attribute. Physical exercise is thought to be associated with vagal hyperactivity that downregulates the funny channel (HCN4 [hyperpolarization activated cyclic nucleotide gated potassium channel 4]) in the sinoatrial node leading to a lower pacemaker rate.¹⁸ However, childhood bradycardia is more likely to be inherited, with a diverse genetic background.¹⁹ Broadly, the genes potentially responsible for bradyarrhythmia can encode ion channels (eg, SCN5A [sodium voltage-gated channel alpha subunit 5]: *SCN5A* gene), gap junction proteins (eg, GJA5 [gap junction protein alpha 5]: *GJA5* gene), calcium handling proteins (eg, RYR2 [ryanodine receptor 2]: *RYR2* gene), and transcription factors (eg, TBX5 [T-box transcription

factor 5]: *TBX5* gene). Thus, by clinically identifying a child with a low RHR, there is a potential to pick an underlying genetic variant predisposing to abnormal cardiac electrophysiology in older age. This is further supported by the fact that in our cohort, childhood bradycardia was not associated with a deficient nutritional status, as low BMI in childhood showed no association with RHR <75 bpm, but high BMI did.

The atrioventricular conduction defects we appraised spanned a broad severity spectrum of bradyarrhythmias, ranging from the fairly benign (first-degree atrioventricular block, Mobitz I second-degree atrioventricular block) to more serious degrees of block (Mobitz II second-degree atrioventricular block or higher). Of the 52 individuals with atrioventricular conduction defects at 60 to 64 years of age, the majority (88%) had benign variants with serious atrioventricular block, accounting for only 12% of cases. From a clinical point of view, this mitigates some of the potential worry for the bradycardic pediatric population, because clearly, the odds of developing higher-order atrioventricular dysfunction, which requires a permanent pacemaker, will be quite low overall. However, future research should identify risk factors predisposing to the development of higher-order atrioventricular dysfunction and should concentrate on developing screening strategies to identify the ones that might.

Pediatricians should search for potential red flags when childhood bradycardia is picked up (eg, abnormal resting ECG, syncope, or family history of cardiomyopathy/cardiac conduction system disease) that could justifiably earmark a smaller number of bradycardic children for closer surveillance. Reassuringly, our data did not indicate that bradycardic children are at higher risk of death or of developing significant cardiac structural or functional abnormalities when compared to their peers with normal RHR.

A strength of the study is the implicit age homogeneity of birth cohort participants enabling age-matching across the analyses. In addition, the NSHD was representative of a British-born population at the time of participant recruitment. As with most epidemiological studies, the main limitation is data missingness. Although we have used multiple imputation to generate covariates, most data missingness comes from missing outcomes that were assessed at 60 to 64 years of age. In addition, missingness at random is one of the core assumptions of multiple imputation, which might not be the case.²⁰ Future studies should aim to include more RHR measurements throughout the life course and account for physiological RHR variability. Prolonged monitoring with 24-hour–7-day Holter monitors or implanted loop recorders would be better suited to assess an individual's chronotropic status. Although we adjusted for the presence of congenital heart disease, atrioventricular and ventricular conduction disease could have been present at baseline, but a baseline ECG was not available for all participants in the 1950s. In addition, the NSHD data collection survey at 6 and 7 years of age did not include information about syncope. Moreover, we do not have any genetic data relevant to the cardiac conduction system in neither the participants nor their biological parents. Selective attendance to follow-up could introduce attrition bias. The childhood analyses lacked adjustment for potentially important covariates such as physical activity, blood pressure in the normal range (as hypertension is rare in children), and cardiovascular disease. Although our study is longitudinal, the evidence presented is insufficient to infer causality.

The prognostic value of RHR in childhood has been a matter of debate. Besides higher risk of atrioventricular conduction defects, we did not find any link between a lower RHR and any of our other outcomes. Thus, individuals who had a RHR in the age-specific bradycardic region were not more likely to die early. In addition, they were not more likely to have a thicker, stiffer, or functionally inefficient heart, because there was no association with EF, LVmass, MCFi and E/e'. However, even though we found no association between childhood bradycardia and higher-order atrioventricular blocks, this result should be interpreted with caution, because only 6 individuals had this outcome.

CONCLUSIONS

Longitudinal birth cohort data, together with a range of sensitivity analyses, indicate that childhood bradycardia trebles the odds of having atrioventricular conduction defects in older age, but it did not influence mortality or older age heart size and function. It is plausible for childhood bradycardia to be genetically determined or the surrogate of an underlying dysfunctional cardiac conduction system established before birth. As 1 in 3 older adults with atrioventricular conduction defects will have had bradycardia in childhood, future research should concentrate on developing screening strategies to identify the children at risk and the potential mechanisms involved.

ARTICLE INFORMATION

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Author Contributions

Dr Topriceanu conceptualized the study design and implementation, analyzed the data, and wrote the article. Dr Moon conceptualized the study design and implementation, and critically reviewed and revised the article. Drs Hughes and Hardy were involved in data acquisition, conceptualized the study design and implementation, and critically reviewed and revised the article. Dr Captur conceptualized the study design and implementation; contributed to the data analysis, interpretation of the results, and article drafting; and critically reviewed and revised the article. Dr Captur is the guarantor of this work, and she attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted. All authors were involved in critically reviewing and revising the article, approved the final version as submitted, and agreed to be accountable for all aspects of the work.

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Disclosures

None.

Supplementary Material

Tables S1–S4

Figure S1

REFERENCES

- Jouven X, Empana JP, Escolano S, Buyck JF, Tafflet M, Desnos M, Ducimetière P. Relation of heart rate at rest and long-term (>20 years) death rate in initially healthy middle-aged men. *Am J Cardiol*. 2009;103:279–283. doi: 10.1016/j.amjcard.2008.08.071
- Bohm M, Cotton D, Foster L, Custodis F, Laufs U, Sacco R, Bath PMW, Yusuf S, Diener HC. Impact of resting heart rate on mortality, disability and cognitive decline in patients after ischaemic stroke. *Eur Heart J*. 2012;33:2804–2812. doi: 10.1093/eurheartj/ehs250
- Paul L, Hastie CE, Li WS, Harrow C, Muir S, Connell JMC, Dominiczak AF, McInnes GT, Padmanabhan S. Resting heart rate pattern during follow-up and mortality in hypertensive patients. *Hypertension*. 2010;55:567–574. doi: 10.1161/HYPERTENSIONAHA.109.144808
- Tresch DD, Fleg JL. Unexplained sinus bradycardia: clinical significance and long-term prognosis in apparently healthy persons older than 40 years. *Am J Cardiol*. 1986;58:1009–1013. doi: 10.1016/S0002-9149(86)80029-7
- Hartaigh BO, Gill TM, Shah I, Hughes AD, Deanfield JE, Kuh D, Hardy R. Association between resting heart rate across the life course and all-cause mortality: longitudinal findings from the Medical Research Council (MRC) National Survey of Health and Development (NSHD). *J Epidemiol Community Health*. 2014;68:883–889. doi: 10.1136/jech-2014-203940
- Baruteau A-E, Perry JC, Sanatani S, Horie M, Dubin AM. Evaluation and management of bradycardia in neonates and children. *Eur J Pediatr*. 2016;175:151–161. doi: 10.1007/s00431-015-2689-z
- Kuh D, Pierce M, Adams J, Deanfield J, Ekelund U, Friberg P, Ghosh AK, Harwood N, Hughes A, Macfarlane PW, et al. Cohort profile: updating the cohort profile for the MRC National Survey of Health and Development: a new clinic-based data collection for ageing research. *Int J Epidemiol*. 2011;40:e1–e9. doi: 10.1093/ije/dyq231
- Prineas RJ. In: Prineas RJ, Crow RS, Zhang ZM, eds. *The Minnesota Code Manual of Electrocardiographic Findings: Including Measurement and Comparison With the Novacode; Standards and Procedures for ECG Measurement in Epidemiologic and Clinical Trials*. 2nd ed. London: Springer; 2010:16–159.
- Ghosh AK, Hardy RJ, Francis DP, Chaturvedi N, Pellerin D, Deanfield J, Kuh D, Mayet J, Hughes AD and Medical Research Council National Survey of Health and Development Scientific and Data Collection T. Midlife blood pressure change and left ventricular mass and remodelling in older age in the British Birth Cohort Study. *Eur Heart J*. 2014;35:3287–3295. doi: 10.1093/eurheartj/ehu389
- Chirinos JA, Segers P, De Buyzere ML, Kronmal RA, Raja MW, De Bacquer D, Claessens T, Gillebert TC, St. John-Sutton M, Rietzschel ER. Left ventricular mass: allometric scaling, normative values, effect of obesity, and prognostic performance. *Hypertension*. 2010;56:91–98. doi: 10.1161/HYPERTENSIONAHA.110.150250
- Rubin J, Steidley DE, Carlsson M, Ong M-L, Maurer MS. Myocardial contraction fraction by M-Mode echocardiography is superior to ejection fraction in predicting mortality in transthyretin amyloidosis. *J Cardiac Fail*. 2018;24:504–511. doi: 10.1016/j.cardfail.2018.07.001
- Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2015;16:233. doi: 10.1093/ehjci/jev014
- Fleming S, Thompson M, Stevens R, Heneghan C, Plüddemann A, Maconochie I, Tarassenko L, Mant D. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. *Lancet*. 2011;377:1011–1018. doi: 10.1016/S0140-6736(10)62226-X
- Royston P, Altman DG. Regression using fractional polynomials of continuous covariates: parsimonious parametric modelling. *Appl Stat*. 1994;43:429–467. doi: 10.2307/2986270
- Patel SR, Breall JA, Diver DJ, Gersh BJ, Levy AP. Bradycardia is associated with development of coronary collateral vessels in humans. *Coron Artery Dis*. 2000;11:467–472. doi: 10.1097/00019501-200009000-00004
- Hatcher CJ, Basson CT. Specification of the cardiac conduction system by transcription factors. *Circ Res*. 2009;105:620–630. doi: 10.1161/CIRCRESAHA.109.204123
- Christoffels VM, Moorman AFM. Development of the cardiac conduction system: why are some regions of the heart more arrhythmogenic than others? *Circ Arrhythm Electrophysiol*. 2009;2:195–207. doi: 10.1161/CIRCEP.108.829341
- D'Souza A, Sharma S, Boyett MR. CrossTalk opposing view: bradycardia in the trained athlete is attributable to a downregulation of a pacemaker channel in the sinus node. *J Physiol*. 2015;593:1749–1751. doi: 10.1113/jphysiol.2014.284356
- Ishikawa T, Tsuji Y, Makita N. Inherited bradyarrhythmia: a diverse genetic background. *J Arrhythm*. 2016;32:352–358. doi: 10.1016/j.joa.2015.09.009
- Dong Y, Peng C-YJ. Principled missing data methods for researchers. *SpringerPlus*. 2013;2:1–17. doi: 10.1186/2193-1801-2-222

SUPPLEMENTAL MATERIAL

Table S1. Missing values per covariate in addition to the complete exposure-outcome pair.

OUTCOME - Childhood RHR pair	Childhood SEP*	BMI at 6 years*	BMI at 7 years*	Congenital heart disease*
EF	20	147	106	54
LVmass_i	22	188	115	62
MCF_i	19	135	99	50
LVEDV_i	20	147	106	54
E/e'	21	158	109	58
AV conduction defects	22	172	116	64
Ventricular conduction defects	22	172	116	64
All-cause mortality	85	555	463	310
Cardiovascular mortality	85	554	461	309

* Data missingness for each covariate per exposure-outcome pair is presented. Results are reported as counts.

RHR, resting heart rate; BMI, body mass index; SEP, socio-economic position; EF, ejection fraction; LVmass_i, left ventricular mass indexed to height^{1.7}; MCF_i, myocardial contraction fraction indexed to height^{1.7}; LVEDV_i, left ventricular end-diastolic volume indexed to height^{1.7}; AV, atrio-ventricular.

Table S2. Complete case analysis: associations between childhood bradycardia and echocardiographic (EF, LVmass_i, MCF_i, LVEDV_i, E/e'), electrocardiographic (AV or ventricular conduction defect) and mortality (all-cause and cardiovascular) outcomes.

OUTCOME	<i>n</i>	Model II*	
		Exponentiated β (95% CI)	<i>p</i> -value
EF	1035	0.99 (0.97, 1.01)	0.547
LVmass _i	1187	0.93 (0.74, 1.02)	0.267
MCF _i	984	0.93 (0.84, 1.03)	0.166
LVEDV _i	1050	1.02 (0.98, 1.06)	0.437
E/e'	1081	1.00 (0.96, 1.04)	0.965
AV conduction defects	1167	3.22 (1.61, 6.20)	0.0006
Ventricular conduction defects	1167	0.73 (0.51, 1.04)	0.087
All-cause mortality	3264	0.94 (0.74, 1.20)	0.623
Cardiovascular mortality	3256	1.29 (0.85, 1.95)	0.241

* Model II was adjusted for sex, childhood socio-economic position, body mass index at 6 and 7 years and for the presence of congenital heart disease for all except the indexed variables (LVmass_i, MCF_i, and LVEDV_i) where adjustment was made for height instead of body mass index.

All reported analyses here consisted of generalized linear models with gamma distribution and log link for EF, LVmass_i, MCF_i, LVEDV_i, and E/e, generalized linear models with binomial distribution and logit link for AV or ventricular conduction defect, and Cox proportional hazard regression models for all-cause and cardiovascular mortality outcomes. Significant *p*-values are highlighted in bold.

β , regression coefficient; CI, confidence interval; EF, ejection fraction; LVmass_i, left ventricular mass indexed to height^{1.7}; MCF_i, myocardial contraction fraction indexed to height^{1.7}; LVEDV_i, left ventricular end-diastolic volume indexed to height^{1.7}; AV, atrio-ventricular.

Table S3. Associations between childhood bradycardia and echocardiographic (EF, LVmass_i, MCF_i, LVEDV_i, E/e'), electrocardiographic (AV or ventricular conduction defect) and mortality (all-cause and cardiovascular) outcomes using random coefficients generalized linear mixed models (GLMMs).

OUTCOME	<i>n</i>	Model II*	
		Exponentiated β (95% CI)	<i>p</i> -value
EF	1035	0.99 (0.97, 1.01)	0.311
LVmass _i	1187	1.03 (0.93, 1.14)	0.582
MCF _i	984	0.94 (0.85, 1.04)	0.250
LVEDV _i	1050	1.03 (1.00, 1.06)	0.069
E/e'	1081	1.00 (0.97, 1.04)	0.883
AV conduction defects	1167	2.50 (1.01, 4.31)	0.047
Ventricular conduction defects	1167	0.75 (0.54, 1.02)	0.070
All-cause mortality	3264	0.95 (0.77, 1.16)	0.610
Cardiovascular mortality	3256	1.11 (0.77, 1.61)	0.580

* Model II was adjusted for sex, childhood socio-economic position, body mass index at 6 and 7 years and for the presence of congenital heart disease for all except the indexed variables (LVmass_i, MCF_i and LVEDV_i) where adjustment was made for height instead of body mass index.

All reported analyses here consisted of generalized linear mixed models with gamma distribution and log link for EF, LVmass_i, MCF_i, LVEDV_i and E/e, generalized linear mixed models with binomial distribution and logit link for AV or ventricular conduction defect, and Cox proportional hazard regression mixed models for all-cause and cardiovascular mortality outcomes.

β , regression coefficient; CI, confidence interval; EF, ejection fraction; LVmass_i, left ventricular mass indexed to height^{1.7}; MCF_i, myocardial contraction fraction indexed to height^{1.7}; LVEDV_i, left ventricular end-diastolic volume indexed to height^{1.7}; AV, atrio-ventricular.

Table S4. Associations between bradycardia and echocardiographic (EF, LVmass_i, MCF_i, LVEDV_i, E/e'), electrocardiographic (AV or ventricular conduction defect) and mortality (all-cause and cardiovascular) outcomes using fractional polynomials.

OUTCOME	Best fitting fractional polynomial formula for the log OR/HR	p-value
EF	None*	N/A
LVmass _i	None*	N/A
MCF _i	None*	N/A
LVEDV _i	None*	N/A
E/e'	None*	N/A
AV conduction defects	$4.37 - \frac{4.85 \cdot RHR \text{ at } 7^\dagger}{100}$	0.0005
Ventricular conduction defects	$0.37 - 0.75 \cdot sex^\dagger$	<0.0001
All-cause mortality	$\frac{1.50 \cdot Childhood SEP^\ddagger}{10}$	<0.0001
Cardiovascular mortality	$\frac{2.35 \cdot Childhood SEP^\ddagger}{10}$	<0.0001

* Neither one of exposures or covariates nor a combination of them made a fractional polynomial or a sum of fractional polynomials best fit with the outcome.

† For the log (odds ratio) of outcome.

‡ For the log (hazard ratio) of outcome.

Sex was recorded as binary variable (1-male and 2-female), childhood socio-economic position was recorded as a categorical variable (1-professional, 2-intermediate, 3- skilled non-manual, 4- skilled manual, 5- partly skilled and 6- non-skilled) and resting heart rate was a continuous variable.

HR, hazard ratio; OR, odds ratio; EF, ejection fraction; LVmass_i, left ventricular mass indexed to height^{1.7}; MCF_i, myocardial contraction fraction indexed to height^{1.7}; LVEDV_i, left ventricular end-diastolic volume indexed to height^{1.7}; AV, atrio-ventricular.

Figure S1. Best fitting fractional polynomial for the associations between resting heart rate and AV conduction defects at 60-64-years of age.

The x-axis consists of resting heart rate (RHR) as a continuous variable, while the y-axis represents the log odds of AV conduction defects. The log odds of AV conduction defects at 60-64 years of age were linearly associated with RHR at 7 years of age using $4.37 - \frac{4.85 \cdot RHR}{100}$ formula. The blue line represents the best fitting fractional polynomial, while the gray area represents the 95% confidence area. RHR at age 6 did not make a fractional polynomial or a sum of fractional polynomial best fit with the outcome of AV conduction defects.

Best fitting fractional polynomial for AV conduction defects at 60–64 years

