Pediatric RESEARCH

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POPULATION STUDY ARTICLE

Electrocardiographic features at rest and during exercise in young adults born preterm below 30 weeks of gestation

Anne-Sophie Gervais[1], Adrien Flahault[1], Tevy Chan[1], Camille Bastien-Tardif[1], Amy Al-Simaani[1], Anik Cloutier[1], Thuy Mai Luu[1], Sylvia Abadir[1,2] and Anne-Monique Nuyt[1]

BACKGROUND: Preterm birth has adverse consequences on the cardiovascular system. Whether premature birth is associated with conduction and repolarisation abnormalities past childhood and into adulthood still needs to be demonstrated.
METHODS: We analyzed the ECG of young adults (23.9 ± 3.1 years) born term (≥37 weeks, $n = 53$) and preterm (<30 weeks, $n = 49$) at rest, peak exercise and 3 min into recovery during an exercise test on a cycle ergometer. We measured PR, QRS and QT intervals, calculated the corrected QT (QTc), and determined blood calcium, magnesium, potassium and fasting glucose.
RESULTS: Mean gestational age was 39.7 ± 1.1 and 27.3 ± 1.3 weeks for the term and the preterm groups, respectively. Apart from an increased heart rate at rest in individuals born preterm, no significant difference was found between both groups for any other ECG parameters at rest. None of the participants had a severely prolonged QTc (>500 ms) at rest; exercise revealed severely prolonged QTc in two participants including one in the preterm group. The use of QT-prolonging medications did not influence ECG parameters in either groups.
CONCLUSIONS: We observed no significant difference in electrocardiographic measurements between young adults born preterm and term. Current results do not support avoidance of QT-prolonging medications in individuals born preterm.

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IMPACT:

- Preterm birth is associated with adverse cardiovascular consequences in early adulthood, but controversial evidence exists regarding differences in electrocardiographic features between young individuals born term and preterm.
- This study aims to assess the differences in electrocardiographic features between young adults born term and preterm, at rest and during exercise training.
- In contrast with previously published data, we observed no significant difference in electrocardiographic measurements between young adults born preterm and term.
- Our study does not support that preterm birth itself exposes young adults to a higher risk of QT prolongation.
- Current results do not support avoidance of QT-prolonging medications in individuals born preterm.

INTRODUCTION

Approximately 15 million babies are born preterm every year.[1] Over the past decades, the survival of preterms has tremendously increased thanks to the progress in perinatal and neonatal care,[2] reaching over 80% of survival of these newborns into adulthood.[3] Our understanding of the long-term consequences of prematurity on adult health is currently limited, although an increasing number of studies have shown an impact of preterm birth on the cardiovascular system. Individuals born preterm have a higher blood pressure[4] and are more likely to have cardiac morphometric changes[5] and dysfunction.[6] They also have increased all-cause and cardiovascular premature mortality.[7]

Both neonates and adults born preterm have altered autonomic control of the cardiovascular system.[8–10] A few studies have evaluated the effects of prematurity or intrauterine growth restriction (IUGR) on the cardiac conduction system at birth as well as in childhood and adulthood. At birth, small for gestational age neonates (with a birth weight <10th percentile for gestation age) had no change in QTc (defined as the QT interval corrected for heart rate (HR) with Bazett's formula, $QTc = QT/\sqrt{RR}$) compared to controls matched for same gestational age (including 65% born preterm) with normal birth weight.[11] In the first weeks following preterm birth, QT interval presented important variations.[12] At 1 month of age, QTc interval was reported to be not significantly different between infants born term and preterm.[10] One study comparing full-term 10-year-old children born low birth weight (<2500 g) to children born with a normal birth weight did not identify any difference in the QTc interval between the two groups.[13] In contrast to these results, an Italian study concerning young adults born preterm has shown increased QTc and PR

[1]Sainte-Justine University Hospital Research Center, University of Montreal, Montreal, QC, Canada and [2]Electrophysiology Service and Adult Congenital Heart Center, Montreal Heart Institute, University of Montreal, Montreal, QC H1T 1C8, Canada
Correspondence: Anne-Monique Nuyt (anne.monique.nuyt@umontreal.ca)
These authors contributed equally: Anne-Sophie Gervais, Adrien Flahault

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intervals associated with increased QT dispersion.[14] In sum, the exact impact of premature birth on QT interval in adulthood remains uncertain.

QT prolongation is associated with an increased risk of torsade de pointes (TdP) ventricular tachyarrhythmias, which are a cause of sudden death.[15,16] Of concern, children and young adults born preterm are more propitious to develop and receive medication for Attention Deficit Hyperactivity Disorder (ADHD)[17–19] and psychiatric disorders[20] and some treatments for these conditions are associated with an increased risk of QTc prolongation and TdP. Although no specific recommendation has been made concerning avoidance of QT-prolonging medications in adults born preterm, Bassareo et al.[14] recommend to use "extreme caution" in case of administration of these medications in adults born preterm.

Approximatively 40% of patients with a long QT syndrome can have a normal QTc at rest.[21] QTc can increase with exercise, which can unmask a concealed congenital long QT syndrome due to a lack of shortening of the absolute QT interval with exercise and tachycardia (shorter RR interval).[21,22] We hypothesized that the alterations of cardiac conduction and repolarisation related to premature birth previously reported during the neonatal period could persist in early adulthood and be demonstrated during an exercise test. In this study, we aimed to assess electrocardiographic changes, particularly QTc prolongation, in a cohort of young adults born preterm, at rest and during exercise.

PATIENTS AND METHODS

Study population

The data was acquired from young adults born preterm at <30 weeks of gestation between 1987 and 1997, admitted to either Sainte-Justine University Hospital, McGill University affiliated Royal Victoria Hospital or Sir Mortimer B. Davis Jewish General Hospital, those hospitals being the three major neonatal intensive care units in Montreal, Quebec. For each participant born preterm, we recruited a control participant born full term (≥37 weeks of gestation) matched for age and sex. Control participants were recruited from friends or siblings of preterm participants or through advertisements using traditional and social media. Full-term controls with a low birth weight (<2500 g) were excluded from the study. Exclusion criteria included pregnancy and conditions that would affect the ability to perform cardiopulmonary exercise testing, including severe neurocognitive impairment and other physical or neuro-sensory conditions. All participants were asymptomatic from a cardiac standpoint. The enrollment period was between October 2014 and July 2019. All consecutive patients who performed the exercise test and had an at rest recorded ECG were included. All participants agreed to be part of this study by giving a written informed consent. Ethics approval was obtained from the participating Hospital Research Ethics Boards.

Data collection

Perinatal and neonatal data was collected from written hospital records. Small for gestational age was defined as a birth weight below the 10th percentile for gestational age according to Hadlock[23] for the preterm group and to Kramer[24] for the full-term group. Health data was obtained by patient questionnaires filled on the day of the exercise test, and confirmed with physician medical records if necessary. On the day of evaluation, each participant was asked to fill questionnaires on their health and medications. Vital signs and anthropomorphic measurements were assessed. A trained clinical nurse measured the blood pressure (BP) as per the Canadian Hypertension Education Program (CHEP) guidelines[25] using an automated oscillometric device (DINAMAP model DPC300M-CF, GE Medical Systems Information Technologies Inc. Milwaukee, WI, USA). Measurements were taken in triplicate after seated rest for 5 min, the last 2 measures averaged and included in our analyses. Health care workers involved in the data collection were blinded to exposure status (preterm vs term).

Laboratory analyses

Morning (after fasting for 12 h overnight) blood sampling was done prior to exercise test. Blood was immediately centrifuged and both plasma and serum were kept at −80 °C for subsequent analyses. All laboratory analyzes shown in this study were measured at the Sainte-Justine University Hospital clinical biochemistry laboratory. Blood potassium, magnesium, glucose and C-reactive protein (CRP) were measured in the serum using an Abbott Architect c8000 clinical chemistry analyzer (Abbott, Mississauga, Ontario, Canada). Ionized calcium was measured in venous whole blood using an ABL800 (Radiometer, Mississauga, Ontario, Canada) blood gaz analyzer. Details concerning laboratory methods and precision of measurements are provided in Supplemental Table 1.

Electrocardiogram and exercise test

After blood collection, all participants were given a meal and waited for at least one hour before undergoing an exercise test on a cycle ergometer at room air (Corrival, Lode, Netherlands). The exercise test was performed as recommended by the American Heart Association.[26] The exercise test consisted of a 3-min resting phase, a 3-min warm-up phase, an effort phase where participant had to pedal with increasing workload every 1 min until maximal effort was reached, and a recuperation phase, which includes 3 min of active rest and 3 min of passive rest without pedaling. The effort phase was stopped when the subject indicated exhaustion or could not maintain a rate of 70 r.p.m. During this test, a continuous 12-lead ECG (GE Case Stress System V6.5 and 6.73, GE Medical Systems Information Technologies GmbH, Freiburg, Germany) was recorded at a speed of 25 mm/s. Electrocardiograms of participants at rest, at maximal effort, and 3 min into recovery were manually analyzed. Tracings were scanned and measurements were done using the magnifier and the ruler function of Adobe Photoshop (Adobe System, San Jose, CA, United States of America, Version 19.1.6), by two trained operators (TC and ASG) blinded to the exposure status, under the supervision of a staff cardiologist (SA). Intra-observer correlation, assessed on a subset of 24 QTc measurements performed twice on separate days, was very good with an intraclass correlation coefficient of 0.94. Three measurements were taken in lead DII or V5 on three QRS complexes at each stage of exercise (rest, peak exercise and 3-minute into recovery), then averaged and used for analyses. The PR interval was measured from the beginning of the P wave to the beginning of the QRS (Q wave, or R wave if Q wave absent). The QRS was measured from the start of the Q wave (or R wave if Q wave absent) to the end of the S wave. The QT was measured from the onset of the QRS to the end of the T wave. This was determined by the intersection between the isoelectric line and the tangent of the steepest part of the T wave's downslope.[27] If present, the U wave was not included in the measurement of the QT. The previous RR interval was measured to correct the QT. QTc interval was calculated using Bazett's formula: $QTc = QT/\sqrt{RR}$. Participants with electrocardiographic abnormalities were asked to come back to the hospital for further investigations. Supplemental Fig. 1 shows how the different intervals were measured on each ECG. ECGs with insufficient quality precluding precise measurement of the intervals were excluded from the analysis.

Statistical analysis

Statistical analyses were performed using R version 3.5.1. For continuous variables, data are presented as means ± standard deviation and between-group comparisons are performed using Student's *t* test. Categorical variables are presented as *n* (%) with between-group comparisons done with the Fisher exact test. In

order to identify and adjust for potential confounders (including age, sex and body mass index), we performed univariate and multivariate linear regressions for continuous parameters. Normality of the distribution of quantitative variables and of residuals of the linear regression models was verified visually.

RESULTS

Study population

The study population comprised 49 adults born preterm (<30 weeks) and 53 adults born term (≥37 weeks) with a mean age of 24 (range, 18–33 years old). Neonatal and adult clinical characteristics of the participants are shown in Table 1. None of the participants had a congenital heart disease, and 5 (13%) of preterm participants had patent ductus arteriosus that had required surgical ligation. Body mass index (BMI) was significantly lower in the preterm group ($p = 0.026$). Blood electrolytes (potassium, ionized calcium, magnesium) levels were within the normal range and similar between the two groups.

Electrocardiographic measurements

Electrocardiographic measurements performed at rest, at peak exercise and 3 min into recovery are shown in Table 2. Compared to adults born term, adults born preterm had a significantly higher resting heart rate (98 ± 22 vs 90 ± 17 bpm, $p = 0.032$). No statistical difference was found in QTc, QRS and PR measurements at rest, peak exercise and 3 min into recovery between adults born preterm and term. None of the participants had a prolonged (>500 ms) QTc at rest, and the proportion of participants with a QTc value at rest above the normal limit of 450 ms in males and 460 ms in females was of 8% ($n = 4$) and 10% ($n = 4$) in the term and the preterm groups, respectively ($p = 1.0$). QTc prolongation occurred in two participants during recovery, one in the preterm group (QTc 3 min into recovery: 527 ms) and one in the term group (QTc 3 min into recovery: 528 ms). Similar results were obtained after adjustment for age, sex, BMI and tobacco smoking.

Impact of neonatal characteristics on electrocardiographic measurements

As shown in Table 3, pregnancy-induced hypertension, preeclampsia and a higher maternal age at delivery were associated with a shorter PR interval at rest in adults born preterm. We observed no other significant association between studied neonatal factors and electrocardiographic measurements at rest in adults born preterm.

Impact of adult characteristic on electrocardiographic measurements

Current tobacco smoking was associated with a longer PR interval in the preterm group only. Each one-year increase in age (in the limited age range of the study) was associated with a 4.6 ms increase in QTc in the term group and a 3.8 ms increase in the preterm group. Each increase in 1 point in BMI was associated with a 5.0 ms increase in QTc in the preterm group, but did not affect QTc in the term group. Each 0.1 mmol/L increase in ionized calcium levels was associated with an increase in 26 ms in PR interval and a decrease in HR of 19 bpm in subjects born preterm, but did not alter electrocardiographic parameters in subjects born term (Table 4).

Use of medications and effects on electrocardiographic measurements

A detailed list of medications used by the study participants is shown in Supplemental Table 2. Individuals born preterm more often used medication for asthma ($n = 9$ (18%) vs $n = 2$ (4%) in the

Table 1. Characteristics of the study participants.

Clinical characteristics	Preterm ($n = 49$)	Term ($n = 53$)	*p*-value
Neonatal characteristics			
Male sex, *n* (%)	19 (39)	21 (40)	1
Gestational age, weeks	27.3 ± 1.3	39.7 ± 1.1	—
Birth weight, g	952 ± 238	3457 ± 437	—
Small for gestational age*, *n* (%)	3 (6)	3 (6)	—
Maternal age, years	30.5 ± 5.0	29.0 ± 4.3	0.215
Maternal PIH, *n* (%)	11 (24)	4 (8)	0.027
Maternal preeclampsia, *n* (%)	10 (22)	4 (8)	0.079
Antenatal steroids, *n* (%)	23 (52)	0 (0)	—
Postnatal steroids, *n* (%)	13 (30)	0 (0)	—
Major neonatal comorbidities†	23 (47)	1 (2)	—
Patent ductus arteriosus surgical ligation	5 (13)	0 (0)	—
Congenital heart disease	0 (0)	0 (0)	—
Adult characteristics			
Age, years	24.2 ± 3.5	23.9 ± 2.9	0.602
Body mass index, kg/m^2	22.5 ± 3.6	24.7 ± 6	0.026
Familial history of long QT syndrome	0 (0)	0 (0)	—
Medication			
Medication for ADHD, *n* (%)	7 (14)	2 (4)	0.084
Antipsychotics, anxiolytics and antidepressants, *n* (%)	4 (8)	2 (4)	0.424
Medications associated with TdP risk‡			0.020
No use of drug affecting QT or TdP risk, *n* (%)	38 (78)	51 (96)	—
No QT prolongation but risk of TdP under certain conditions (i.e., causing an electrolyte disturbance), *n* (%)	5 (10)	2 (4)	—
QT prolongation and possible risk of TdP, *n* (%)	3 (6)	0 (0)	—
QT prolongation with known risk of TdP, *n* (%)	3 (6)	0 (0)	—
SBP on study day, mmHg	118 ± 13	117 ± 13	0.655
DBP on study day, mmHg	70 ± 9	67 ± 9	0.170
Blood biochemical assays			
Potassium, mmol/L	3.9 ± 0.2	4.0 ± 0.2	0.081
Range (min–max)	3.6–4.6	3.6–4.4	—
Ionized calcium, mmol/L	1.18 ± 0.03	1.19 ± 0.04	0.633
Range (min–max)	1.09–1.27	1.08–1.25	—
Magnesium, mmol/L	0.8 ± 0.06	0.81 ± 0.06	0.298
Range (min–max)	0.70–0.95	0.65–0.95	—
Fasting glucose, mmol/L	4.8 ± 0.4	4.9 ± 0.6	0.427
Range (min–max)	3.4–6.8	3.9–5.3	—
CRP, mg/L	2.6 ± 4.1	4.0 ± 7.6	0.253
Range (min–max)	0.2–46.5	0.2–18.3	—

Data are presented as mean ± SD or *n* (%). *ADHD* attention deficit hyperactivity disorder, *CRP* highly sensitive C-reactive protein, *DBP* diastolic blood pressure, *PIH* pregnancy induced hypertension (hypertension and/or preeclampsia), *SBP* systolic blood pressure, *TdP* torsade de pointes. *Small for gestational age: weight below the 10th percentile for gestational age according to Kramer (term group) or Hadlock (preterm group). †Major neonatal comorbidities include bronchopulmonary dysplasia (oxygen requirement at 36 weeks post menstrual age); severe brain injury (intraventricular hemorrhage (grade ≥ 3) or cystic periventricular leukomalacia); retinopathy of prematurity (grade ≥ 3); patent ductus arteriosus surgical ligation; necrotizing enterocolitis; confirmed neonatal sepsis; 1 participant from the term group had a history of neonatal sepsis. ‡According to CredibleMeds.org.

term and the preterm group, respectively, $p = 0.024$), and we observed a trend towards a higher rate of treatment for psychiatric disorders and ADHD in the preterm group ($n = 8$ (16%) vs $n = 3$ (6%), $p = 0.11$). The number of participants taking medications associated with an increased risk of TdP was significantly higher in the preterm group ($n = 11$ (22%) vs $n = 2$ (4%), $p = 0.006$). The use of medications associated with a risk of TdP did not significantly alter any of the ECG parameters at rest in the term or the preterm groups. The two participants identified with QTc prolongation during recovery did not take any QT-prolonging medication.

Table 2. Electrocardiography measurements.

Outcome measurements	Preterm	Term	*p*-value	Adjusted *p*-value[§]
At rest	$n = 49$	$n = 53$	—	—
HR, bpm	98 ± 22	90 ± 17	0.032	0.001
QTc, ms	408 ± 34	409 ± 31	0.899	0.794
QTc mild increase*	4 (10)	4 (8)	1	—
QTc severe increase[&]	0 (0)	0 (0)	1	—
QRS, ms	85 ± 10	84 ± 13	0.684	0.600
PR, ms	141 ± 27	149 ± 26	0.128	0.064
At peak exercise	$n = 38$	$n = 41$	—	—
HR, bpm	180 ± 14	178 ± 13	0.631	0.335
QTc, ms	387 ± 34	387 ± 23	0.906	0.847
QTc mild increase*	0 (0)	0 (0)	1	—
QTc severe increase[&]	0 (0)	0 (0)	1	—
QRS, ms	75 ± 12	75 ± 10	0.773	0.988
PR, ms	104 ± 18	106 ± 15	0.683	0.634
At 3 min of recovery	$n = 35$	$n = 43$	—	—
HR, bpm	142 ± 16	138 ± 17	0.28	0.031
QTc	418 ± 35	409 ± 34	0.298	0.219
QTc mild increase*	3 (9)	1 (2)	0.31	—
QTc severe increase[&]	1 (3)	1 (2)	1	—
QRS, ms	83 ± 11	79 ± 14	0.271	0.169
PR, ms	131 ± 18	133 ± 16	0.658	0.254

Data are presented as mean ± SD or *n* (%). *p*-Value calculated using Student's *t*-test or the Fisher exact test. *HR* heart rate, *QTc* QT corrected with Bazett's formula. *QTc mild increase: QTc > 450 ms (men) or > 460 ms (females) but <500 ms; [&]QTc severe increase: QTc > 500 ms;[§]Adjusted *p*-value: adjusted for age, sex, BMI and current tobacco smoking using a multivariate linear model.

DISCUSSION

In this study, we did not find significant alterations of electrocardiographic measures in young adults born preterm, when compared to full-term born controls. Participants using potentially QT-prolonging medications did not have significantly higher QTc intervals in either groups. A higher BMI was associated with a longer QTc in the preterm group only.

We found a higher resting heart rate and diastolic blood pressure in adults born preterm, compared to those born term, which is consistent with previously reported studies.[4,28,29] However, at maximal effort and after 3 min of recovery, heart rate was similar between groups. These results differ slightly from Haraldsdottir et al.[29] who also reported similar maximal heart rate but slower recovery heart rate 2 min after maximal exercise in a smaller group of young adults born preterm ($n = 12$) vs term. No other difference was found in the measured ECG parameters at rest between adults born preterm and term, including in PR and QTc intervals.

These results are in line with previous findings from studies conducted during the neonatal period[10–12] and during childhood,[13] which did not identify an increased risk for QT prolongation in individuals born preterm. However, in contrast with our findings, Bassareo et al.[14] previously reported significantly shorter PR (by 22.7 ms) and increased QTc (by 47.1 ms) intervals in 24 young adults (23.2 ± 3.3 years) born preterm (mean gestational age, 27.8 weeks) vs term in Italy. In our study, individuals who experienced severe complications from preterm birth, including bronchopulmonary dysplasia, were not found to be at higher risk of QTc interval prolongation than the ones with less severe complications during the neonatal period. The proportion of participants with a QTc value above the normal limit was similar between the two groups. A significant QTc prolongation occurred in recovery in 2 participants, one preterm and one term, who did not have any history of syncope and did not show any symptom during exercise. These participants have been referred to the cardiology clinic for further investigations. Patients characteristics in our study were very similar to those from Bassareo et al.,[14] although a higher proportion of males was included in our study.

As the participants from our study were mainly Caucasians from the province of Quebec, Canada, it is possible that the discrepancies between the two studies are the results of differences in population and genetic backgrounds. While the risk of having a congenital long QT syndrome is 1:2000 in the general population, this risk increases up to 50% in case of a family

Table 3. Impact of neonatal factors on electrocardiography measurements in young adults born preterm.

Neonatal characteristics	HR, bpm	QTc, ms	QRS, ms	PR, ms
	B (95% CI)	B (95% CI)	B (95% CI)	B (95% CI)
Gestational age, weeks	−1.77 (−6.73, 3.19)	−0.55 (−8.08, 6.99)	1.22 (−0.81, 3.24)	−5.58 (−11.81, 0.65)
Antenatal corticosteroids	−5.21 (−18.56, 8.14)	−0.23 (−20.52, 20.07)	−0.69 (−6.10, 4.73)	−10.98 (−28.43, 6.47)
Postnatal corticosteroids	6.71 (−8.25, 21.66)	13.80 (−8.68, 36.29)	−5.83 (−11.52, −0.13)	7.41 (−11.65, 26.48)
Major neonatal comorbidity[§]	9.82 (−2.36, 22.01)	3.75 (−15.83, 23.32)	−4.89 (−9.91, 0.12)	14.18 (−1.47, 29.82)
Birth weight percentile	−0.12 (−0.57, 0.34)	−0.02 (−0.74, 0.69)	−0.05 (−0.24, 0.14)	−0.18 (−0.81, 0.45)
Pregnancy-induced hypertension	3.54 (−12.08, 19.17)	−7.14 (−32.46, 18.19)	1.83 (−4.44, 8.09)	−22.88 (−41.44, −4.32)*
Preeclampsia	3.32 (−13.34, 19.99)	−7.14 (−32.46, 18.19)	1.56 (−5.13, 8.25)	−24.20 (−44.07, −4.34)*
Maternal age at delivery	−0.27 (−1.91, 1.37)	0.11 (−2.12, 2.33)	0.22 (−0.45, 0.90)	−2.56 (−4.50, −0.62)*

B regression coefficients. *$p < 0.05$. [§]Major neonatal morbidities as defined in Table 1.

Table 4. Impact of clinical and biological data on electrocardiography measurements in young adults born preterm and term.

Current characteristics	HR, bpm	QTc, ms	QRS, ms	PR, ms
	B (95% CI)	B (95% CI)	B (95% CI)	B (95% CI)
Preterm				
Age, year	−0.38 (−2.20, 1.43)	3.81 (0.71, 6.90)*	0.47 (−0.36, 1.30)	−0.30 (−2.79, 2.20)
Male sex	−12.32 (−24.65, 0.02)	−12.93 (−33.16, 7.31)	9.76 (4.53, 14.99)*	−2.28 (−18.28, 13.73)
BMI, kg/m^2	2.02 (0.36, 3.68)*	4.98 (2.51, 7.44)*	−0.40 (−1.20, 0.40)	−0.33 (−2.50, 1.83)
Medication affecting QT	−2.75 (−17.71, 12.21)	−18.10 (−43.64, 7.44)	−4.43 (−11.23, 2.38)	−3.02 (−21.39, 15.35)
Current tobacco smoking	−13.5 (−28.0, 0.94)	7.24 (−16.01, 30.48)	1.04 (−5.87, 7.96)	18.8* (1.27, 36.37)
SBP, mmHg	0.49 (0.04, 0.95)*	0.31 (−0.43, 1.04)	0.24 (0.03, 0.45)*	−0.26 (−0.85, 0.32)
DBP, mmHg	1.06 (0.44, 1.68)*	0.43 (−0.66, 1.51)	0.02 (−0.30, 0.34)	−0.69 (−1.53, 0.16)
Fasting glucose, mmol/L	4.49 (−13.17, 22.15)	23.91 (−5.52, 53.33)	−0.53 (−8.90, 7.85)	2.72 (−20.83, 26.27)
Potassium levels, 0.1 mmol/L	0.32 (−2.83, 3.46)	3.81 (−1.09, 8.71)	−0.23 (−1.72, 1.27)	−1.44 (−5.48, 2.60)
Ionized calcium levels, 0.1 mmol/L	−18.95 (−36.9, −0.94)*	9.05 (−19.04, 37.14)	7.18 (−1.60, 15.96)	25.50 (2.16, 48.84)*
Magnesium levels, 0.1 mmol/L	−5.13 (−14.65, 4.40)	13.62 (−2.49, 29.74)	1.31 (−3.23, 5.86)	−0.14 (−13.03, 12.75)
CRP levels, mg/L	0.93 (−0.56, 2.42)	2.51 (−0.33, 5.34)	−0.15 (−0.87, 0.56)	1.18 (−0.74, 3.10)
Term				
Age, year	1.63 (0.02, 3.24)	4.58 (1.81, 7.35)*	−0.16 (−1.37, 1.05)	1.62 (−0.84, 4.08)
Male sex	−13.0 (−22.0, −4.01)*	−25.0 (−40.8, −9.19)*	6.08 (−0.71, 12.88)	1.87 (−12.61, 16.34)
BMI, kg/m^2	0.94 (0.18, 1.69)*	1.18 (−0.20, 2.55)	0.12 (−0.45, 0.70)	0.13 (−1.06, 1.33)
Medication affecting QT	14.44 (−10.02, 38.91)	25.77 (−17.49, 69.02)	−9.35 (−27.12, 8.43)	8.07 (−29.06, 45.19)
Current tobacco smoking	−11.7 (−27.5, 4.13)	−17.2 (−45.4, 11.1)	0.82 (−10.9, 12.52)	1.94 (−22.29, 26.18)
SBP, mmHg	0.06 (−0.30, 0.42)	0.15 (−0.50, 0.81)	0.21 (−0.04, 0.47)	0.36 (−0.17, 0.89)
DBP, mmHg	0.56 (0.06, 1.06)*	0.75 (−0.19, 1.69)	0.07 (−0.30, 0.45)	0.52 (−0.25, 1.29)
Fasting glucose, mmol/L	1.45 (−6.83, 9.72)	−8.14 (−22.73, 6.45)	0.44 (−5.47, 6.35)	−4.53 (−16.95, 7.89)
Potassium levels, 0.1 mmol/L	1.39 (−0.54, 3.33)	1.83 (−1.76, 5.42)	−0.23 (−1.66, 1.19)	−1.00 (−3.95, 1.94)
Ionized calcium levels, 0.1 mmol/L	−7.34 (−19.57, 4.89)	−5.41 (−27.34, 16.51)	−1.05 (−10.06, 7.96)	9.09 (−9.28, 27.47)
Magnesium levels, 0.1 mmol/L	0.27 (−7.89, 8.43)	3.17 (−11.84, 18.17)	4.16 (−1.65, 9.96)	2.30 (−9.93, 14.53)
CRP levels, mg/L	0.25 (−0.37, 0.88)	0.30 (−0.80, 1.41)	−0.02 (−0.47, 0.44)	0.42 (−0.51, 1.36)

Coefficients for blood electrolytes (potassium, calcium and magnesium) are shown for each 0.1 mmol/L increase. *B* regression coefficients, *BMI* body mass index, *CRP* C-reactive protein, *DBP* diastolic blood pressure, *SBP* systolic blood pressure. *$p < 0.05$.

history of clinically established and genetically confirmed long QT syndrome.[30] In fact, Bassareo et al identified a clustering of QT interval prolongation among siblings from the same family.[14] Taken together, Bassareo's and the current study cannot conclude that preterm birth itself may expose young adults to a higher risk of QT prolongation. It is possible that specific genetic backgrounds could increase both risks of preterm birth and cardiac disease including QT prolongation.[31,32]

As cardiomyocyte polarization and depolarization is highly dependant on ion gradients, we investigated whether blood potassium, ionized calcium and magnesium levels were associated with changes in electrocardiographic intervals. Blood potassium and magnesium levels were all within the normal range and variations in these electrolytes were not associated with electrocardiographic changes. Hypercalcemia can be associated with an increase in the PR interval.[33] In our study, higher blood ionized calcium levels were associated with slightly longer PR intervals and a lower heart rate in individuals born preterm, but not term. Although statistically significant, the clinical relevance of these finding remains uncertain since both ionized calcium and PR interval values in the preterm group were within normal range.

Previous studies have associated obesity with QT and QTc prolongation in the general population.[34,35] Higher BMI and age were associated with a QTc increase in the individuals born preterm only. An older age and female sex were associated with a higher QTc in the term group. Moreover, the BMI in the preterm group was significantly lower than the term group. Tobacco smoking was associated with a longer PR interval in the preterm group. We thus conducted a multivariate analysis that showed no difference in electrocardiographic features between the term and the preterm group even after adjustment for age, sex, BMI and tobacco smoking, except for heart rate.

Preterm birth is associated with alterations in cardiac structure and function, including cardiac hypertrophy,[5] changes that are aggravated with exercise.[36] Left ventricular hypertrophy has been associated with changes in cardiac repolarization.[37] Since participants in our study were 21–32 years old, further studies evaluating electrocardiographic features in older adults born preterm might therefore be required since QT prolongation on ECG may be initially concealed and be revealed only later in life.[38] QT prolongation is associated with a risk of TdP, and this risk in increased with QT-prolonging drugs. We did not find however any significant effect of the use of such medications on electrocardiographic measurements.

Individuals born preterm more often used medication for asthma, psychiatric and ADHD drugs. This is in line with the literature, which shows a higher rate of airflow limitation,[39] of hypertension,[4] of psychiatric disorders[20] and of ADHD[17–19] in those born preterm. Of all drugs used by the study participants, those associated with an increased risk of TdP were mostly psychiatric and ADHD drugs, resulting in a higher rate of young individuals born preterm receiving QT-prolonging medication.

Our study has several limitations. First, our study included a relatively low number of participants, and 23% (21% and 26% in

the term and the preterm groups, respectively) of ECGs performed during exercise could not be analyzed due to movement artefacts. Subtle changes in electrocardiographic features may not have been identified by our study. Indeed, post-hoc power calculations show that our study would have had 80% power to detect a difference of at least 18 ms in QTc between the two groups. However, the only other study, to our knowledge, reporting on QTc in young adults born preterm had included an even lower number of participants, and reported a 47 ms difference in QTc intervals between the two groups, which our study would have had power to detect.[14] Second, use of medication was self-declared by the participants and we did not assess treatment observance; thus, the true effect of potentially QT-prolonging drugs may have been under measured. In addition, it is possible that participants recently received or had been receiving a short course of medication (ie antibiotics) that would not have been declared by the participant and may have affected the electrocardiogram. As participants were specifically asked to mention all current and previous medications within the past year, it is unlikely this may have significantly altered our results.

We found no significant difference in electrocardiographic measurements between young adults born preterm and term, except for the higher resting heart rate in individuals born preterm. However, we showed that electrolyte imbalance and increase in BMI in individuals born preterm had a stronger association with QTc prolongation than in those born term. These observations require confirmation in other cohorts. Surveillance of electrolyte levels and ECG could be considered when prescribing QT-prolonging medications in young adults born preterm. Results from this study, however, do not support avoidance of these medications in adults born preterm.

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AUTHOR CONTRIBUTIONS

T.M.L. and A.M.N. conceived and designed the study and obtained the funding. All authors collected the data. A.S.G., A.F., T.C., S.A. and A.M.N. designed and performed the analysis. All authors drafted the manuscript, approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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ADDITIONAL INFORMATION

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REFERENCES

1. Howson, C. P. et al. Born too soon: preterm birth matters. *Reprod. Health* **10**(Suppl 1), S1 (2013).
2. Glass, H. C. et al. Outcomes for extremely premature infants. *Anesth. Analg.* **120**, 1337–1351 (2015).
3. Helenius, K. et al. Survival in very preterm infants: an international comparison of 10 national neonatal networks. *Pediatrics* **140**, e20171264 (2017).
4. Hovi, P. et al. Blood pressure in young adults born at very low birth weight: adults born preterm international collaboration. *Hypertension* **68**, 880–887 (2016). 1979.
5. Lewandowski, A. J. et al. Preterm heart in adult life: cardiovascular magnetic resonance reveals distinct differences in left ventricular mass, geometry, and function. *Circulation* **127**, 197–206 (2013).
6. Lewandowski, A. J. et al. Right ventricular systolic dysfunction in young adults born preterm. *Circulation* **128**, 713–720 (2013).
7. Crump, C., Sundquist, K., Sundquist, J. & Winkleby, M. A. Gestational age at birth and mortality in young adulthood. *JAMA* **306**, 1233–1240 (2011).
8. Fyfe, K. L., Yiallourou, S. R., Wong, F. Y. & Horne, R. S. C. The development of cardiovascular and cerebral vascular control in preterm infants. *Sleep. Med Rev.* **18**, 299–310 (2014).
9. Mathewson, K. J. et al. Autonomic functioning in young adults born at extremely low birth weight. *Glob. Pediatr. Health* **2**, 2333794X15589560 (2015).
10. Kojima, A. et al. Maturation of the QT variability index is impaired in preterm infants. *Pediatr. Cardiol.* **39**, 902–905 (2018).
11. Fouzas, S. et al. Heterogeneity of ventricular repolarization in newborns with intrauterine growth restriction. *Early Hum. Dev.* **90**, 857–862 (2014).
12. Séguéla, P.-E., Rozé, J.-C. & Gournay, V. Evolution of the QT interval in premature infants: a preliminary study. *Cardiol. Young* **22**, 430–435 (2012).
13. Akyuz, A. et al. Does low birth weight affect P-wave and QT dispersion in childhood? *Pacing Clin. Electrophysiol.* **36**, 1481–1487 (2013).
14. Bassareo, P. P. et al. Significant QT interval prolongation and long QT in young adult ex-preterm newborns with extremely low birth weight. *J. Matern. Fetal Neonatal Med.* **24**, 1115–1118 (2011).
15. Uvelin, A., Pejaković, J. & Mijatović, V. Acquired prolongation of QT interval as a risk factor for torsade de pointes ventricular tachycardia: a narrative review for the anesthesiologist and intensivist. *J. Anesth.* **31**, 413–423 (2017).
16. El-Sherif, N., Turitto, G. & Boutjdir, M. Congenital Long QT syndrome and torsade de pointes. *Ann. Noninvasive Electrocardiol.* **22**, e12481 (2017).
17. James, S.-N. et al. Association of preterm birth with ADHD-like cognitive impairments and additional subtle impairments in attention and arousal malleability. *Psychol. Med.* **48**, 1484–1493 (2018).
18. Sucksdorff, M. et al. Preterm birth and poor fetal growth as risk factors of attention-deficit/ hyperactivity disorder. *Pediatrics* **136**, e599–e608 (2015).
19. Lindström, K., Lindblad, F. & Hjern, A. Preterm birth and attention-deficit/hyperactivity disorder in schoolchildren. *Pediatrics* **127**, 858–865 (2011).
20. Lindström, K., Lindblad, F. & Hjern, A. Psychiatric morbidity in adolescents and young adults born preterm: a Swedish national cohort study. *Pediatrics* **123**, e47–e53 (2009).
21. Horner, J. M., Horner, M. M. & Ackerman, M. J. The diagnostic utility of recovery phase QTc during treadmill exercise stress testing in the evaluation of long QT syndrome. *Heart Rhythm* **8**, 1698–1704 (2011).
22. Bika Lele, E. C. et al. [Effect of intermittent variable intensity exercise on QT variation and risk of sudden cardiac death among Cameroonian school adolescents]. *Ann. Cardiol. Angeiol. (Paris)* **67**, 48–53 (2018).
23. Hadlock, F. P., Harrist, R. B. & Martinez-Poyer, J. In utero analysis of fetal growth: a sonographic weight standard. *Radiology* **181**, 129–133 (1991).
24. Kramer, M. S. et al. A new and improved population-based Canadian reference for birth weight for gestational age. *Pediatrics* **108**, E35 (2001).
25. Daskalopoulou, S. S. et al. The 2015 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. *Can. J. Cardiol.* **31**, 549–568 (2015).
26. Balady, G. J. et al. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation* **122**, 191–225 (2010).
27. Postema, P. G., De Jong, J. S. S. G., Van der Bilt, I. A. C. & Wilde, A. A. M. Accurate electrocardiographic assessment of the QT interval: teach the tangent. *Heart Rhythm* **5**, 1015–1018 (2008).
28. Paquette, K. et al. Kidney size, renal function, Ang (Angiotensin) peptides, and blood pressure in young adults born preterm. *Hypertension* **72**, 918–928 (2018). 1979.
29. Haraldsdottir, K. et al. Heart rate recovery after maximal exercise is impaired in healthy young adults born preterm. *Eur. J. Appl Physiol.* **119**, 857–866 (2019).
30. Schwartz, P. J. & Ackerman, M. J. The long QT syndrome: a transatlantic clinical approach to diagnosis and therapy. *Eur. Heart J.* **34**, 3109–3116 (2013).
31. Boivin, A. et al. Risk for preterm and very preterm delivery in women who were born preterm. *Obstet. Gynecol.* **125**, 1177–1184 (2015).

32. Zhang, G. et al. Genetic associations with gestational duration and spontaneous preterm birth. *N. Engl. J. Med* **377**, 1156–1167 (2017).
33. Douglas, P. S., Carmichael, K. A. & Palevsky, P. M. Extreme hypercalcemia and electrocardiographic changes. *Am. J. Cardiol.* **54**, 674–675 (1984).
34. Kumar, T. et al. Study of the effect of obesity on QT-interval among adults. *J. Fam. Med Prim. Care* **8**, 1626–1629 (2019).
35. Inanir, M. et al. Evaluation of electrocardiographic ventricular repolarization parameters in extreme obesity. *J. Electrocardiol.* **53**, 36–39 (2018).
36. Huckstep, O. J. et al. Physiological stress elicits impaired left ventricular function in preterm-born adults. *J. Am. Coll. Cardiol.* **71**, 1347–1356 (2018).
37. Mayet, J. et al. Left ventricular hypertrophy and QT dispersion in hypertension. *Hypertens. Dallas Tex.* **28**, 791–796 (1996). 1979.
38. Reardon, M. & Malik, M. QT interval change with age in an overtly healthy older population. *Clin. Cardiol.* **19**, 949–952 (1996).
39. Doyle, L. W. et al. Ventilation in extremely preterm infants and respiratory function at 8 years. *N. Engl. J. Med* **377**, 329–337 (2017).