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ORIGINAL RESEARCH

Low Birth Weight Increases the Risk of Sudden Cardiac Death in the Young: A Nationwide Study of 2.2 Million People

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BACKGROUND: Sudden cardiac death (SCD) constitutes a major health problem worldwide. We investigated whether birth weight (BW), small for gestational age (SGA), and large for gestational age are associated with altered risk of SCD among the young (aged 1–36 years).

METHODS AND RESULTS: We included all people born in Denmark from 1973 to 2008 utilizing the Danish Medical Birth Register. All SCDs in Denmark in 2000 to 2009 have previously been identified. We defined 5 BW groups, SGA, and large for gestational age as exposure and SCD as the outcome. We estimated the age-specific relative risk of SCD with 95% CI. Additionally, we investigated if SGA and large for gestational age are associated with pathological findings at autopsy. The study population for the BW analyses comprised 2 234 501 people with 389 SCD cases, and the SGA and large for gestational age analyses comprised 1 786 281 people with 193 SCD cases. The relative risk for SCD was 6.69 for people with BW between 1500 and 2499 g (95% CI, 2.38–18.80, $P<0.001$) and 5.89 for people with BW ≥4500 g (95% CI, 1.81–19.12, $P=0.003$) at age 5 years. BW 2500 to 3400 g was the reference group. Compared with an appropriate gestational age, the relative risk for SGA was 2.85 (95% CI, 1.35–6.00, $P=0.006$) at age 10 years. For the autopsied cases, the relative risk of sudden arrhythmic death syndrome at age 5 years was 4.19 for SGA (95% CI, 1.08–16.22, $P=0.038$).

CONCLUSIONS: We found an association between BW and SCD in the young, with an increased risk among SGA infants. In addition, we found an association between SGA and sudden arrhythmic death syndrome.

Key Words: birth weight ■ large for gestational age ■ small for gestational age ■ sudden arrhythmic death syndrome ■ sudden cardiac death

Sudden cardiac death (SCD) is a tragic event and constitutes a major health problem. It accounts for 50% of all cardiac deaths in developed countries, resulting in millions of deaths worldwide each year.[1,2] SCD is commonly defined as a sudden, natural, and unexpected death because of an acute change in cardiovascular status.[3–5] Within the younger population (aged 1–35 years) in Denmark, approximately 7% of all deaths can be attributed to SCD, and cardiac arrhythmia is reported as the most frequent cause of sudden natural death in people aged ≤35 years in Denmark and Australia.[4,6] In comparison, around 80% of SCDs in the adult population are caused by coronary artery disease.[7] Despite the well-documented relationship between known medical conditions and SCD, ≈50% of out-of-hospital sudden cardiac arrest survivors are individuals with no clinical history of cardiac disease.[8] The diversity of pathologies and mechanisms

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CLINICAL PERSPECTIVE

What Is New?

- To our knowledge, no other studies have investigated an association between birth weight and the risk of sudden cardiac death (SCD) among the young.
- We used Danish National Registers in this nationwide study of 2.2 million people. We investigated and found an association between birth weight and the risk of SCD among people aged 1 to 36 years.
- We accounted for the gestational age and found an increased risk of SCD among small for gestational age infants. Additionally, we found an association between small for gestational age and sudden arrhythmic death syndrome in the young.

What Are the Clinical Implications?

- Because birth weight and size for gestational age might predict the risk of SCD later in life, our results may contribute to identifying people at risk and improve the prevention of SCD in the future.

Nonstandard Abbreviations and Acronyms

BW	birth weight
ISCED	International Standard Classification of Education
MBR	Medical Birth Register
SCD	sudden cardiac death

in addition to the lack of documented risk factors present challenges in the development of preventative initiatives of SCD. To understand the process of disease, investigators have suggested that early stages of fetal development and conditions during pregnancy have an impact, resulting in the fetal origins of the adult disease hypothesis.[9] This theory proposes that conditions during sensitive periods of development during pregnancy have permanent effects and may predispose to disease later in life. It has led to research investigating the possible influence of early life factors affecting the fetal growth parameter birth weight (BW) on the development of adult disease. Obesity, hypertension, and type 2 diabetes mellitus have all been associated with BW outside the normal range, and researchers have reported an inverse association between BW and the risk of ischemic heart disease later in life.[10–14] Additionally, an association between BW and atrial fibrillation has previously been reported.[15] To our knowledge, however, no previous studies have investigated an association between BW and SCD in the young.

Prematurity causes low BW, which is closely related to morbidity and mortality.[16] Because BW is determined by the length of gestation and intrauterine growth, gestational age should be taken into consideration when studying the effect of intrauterine growth on BW. On this basis, we found it pertinent to investigate whether small for gestational age (SGA) infants and large for gestational age (LGA) infants have an increased risk of SCD. We wanted to explore whether BW can alter the risk of SCD, potentially contributing to improving diagnostics and prevention of SCD in the future.

METHODS

Study Design

This was a nationwide retrospective study using data from the Danish Medical Birth Register (MBR) as well as 2 previous Danish studies identifying all SCDs in the Danish population aged 1 to 35 years between 2000 and 2009, and 36 to 49 years between 2007 and 2009.[4,5,17] According to the Danish National Committee on Health Research Ethics, register-based research projects that are based on pure data are not subject to notification.[18]

Study Population

We included all people born between January 1, 1973 and December 31, 2008 who survived their first year of life. The observation period was January 1, 2000 until December 31, 2009. We excluded all individuals who died before the observation period or if the BW was not accessible in the MBR. We censored individuals who emigrated from Denmark (ie, people who have given up their residence in Denmark and moved abroad for at least 6 months).[19] We included BWs between 125 and 7000 g and birth lengths between 25 and 70 cm, and excluded gestational periods over 43 full weeks (43+6).[20]

Data Sources

All data and supporting materials are available within the article and the supplementary material. The methods of the previous Danish SCD studies in the young have been thoroughly described.[4,5] In brief, all cases of SCD in the young population aged 1 to 35 years between 2000 and 2009, and 36 to 49 years between 2007 and 2009 were identified on the basis of the availability of data from nationwide administrative health registers, with registration of all in- and outpatient activity in Danish hospitals and emergency rooms, death

certificates, autopsy reports, medical records, and discharge summaries.

Data Collection: Danish Registers, Death Certificates, and Conduction of Autopsies

All Danish citizens are assigned a unique civil registration number that is used for all healthcare services and linked to all national registers. Information on the Danish population such as births, deaths, and migration to and from Denmark is registered nationally and updated continuously, ensuring minimal loss to follow-up. The MBR contains information on all births in Denmark since 1973, and the content, coverage, and validity have previously been described.[17] The accuracy of BW registration has changed over time; during 1973 to 1978 BW was registered in intervals of 500 g, during 1979 to 1990 BW was registered in intervals of 10 g, and since 1991 BW is registered in exact grams. The Danish National Patient Register contains information on all inpatient activity since 1977 and outpatient activity since 1994.[21] Diagnosis codes are coded according to the *International Classification of Diseases* (*ICD*) for each visit.[22] The Danish Population Education Register was used for information on maternal educational level.[23] When a person dies within the Danish borders, a death certificate is always issued by a medical doctor, and the death is registered in the Danish Cause of Death Register.[24] All primary and contributing causes of death are available in the registry. The Danish death certificates include a supplemental information field describing the circumstances about the death and is therefore highly informative. All death certificates were retrieved digitally and were read independently by 2 physicians to identify sudden and unexpected deaths.[4,5] In case of a discrepancy, a consensus was reached after re-evaluating the circumstances surrounding the death. Additionally, when a person is found dead or the death is sudden or unexpected, an external examination is mandatory by Danish law. It is performed by medical doctors and the police, and documented in the supplemental information field. If the cause of death cannot be established after the external examination, the police can request a forensic autopsy. In cases where the police decide not to perform a forensic autopsy, medical doctors or relatives can request a hospital autopsy. Medical records and discharge summaries were accessed digitally.[4,5] Discharge summaries describe the circumstances of the death and include treatment and management from prehospital trauma, emergency room, and hospital department. Medical records and discharge summaries were perused to determine whether the death was sudden and unexpected in cases where the death certificate did not clearly state this matter.[4,5] Well-known maternal conditions influence the intrauterine growth and affect the BW in offspring.[25] We used the National Patient Register to obtain information on maternal comorbidities and performed subgroup analyses where we directly adjusted for these (see Table S1 for *ICD* codes). In addition to the National Patient Register, the Danish National Prescription Registry was used to determine diabetes mellitus and hypertension, with pharmacotherapy defined as claimed drug prescriptions within 12 months before giving birth (see Table S2 for Anatomical Therapeutic Chemical codes).[26] A similar approach has previously been described.[27,28]

Definitions

We divided BW into 5 groups for our analyses: <1500, 1500 to 2499, 2500 to 3499, 3500 to 4499, and ≥4500 g. We considered births between week 37+0 and 43+6 to be at term. We defined SGA infants as infants with BW <10th percentile for a given week of gestation, and LGA infants as infants with BW >90th percentile for a given week of gestation.[29] Infants with BW between the 10th and 90th percentile were defined as appropriate for gestational age. We used maternal educational level defined as the highest completed education when the child was aged 5 years as a measurement of socioeconomic status. Educational level was categorized according to the International Standard Classification of Education (ISCED) 0 to 8.[30] A 10-year education is compulsory in Denmark. The ISCED level 0 to 2 correspond to early childhood education, primary education, and lower secondary education; ISCED level 3 corresponds to upper secondary education; ISCED levels 5 to 6 correspond to bachelor's or equivalent education level; and ISCED levels 7 to 8 correspond to master's or equivalent level or doctoral or equivalent level. The ISCED level 4 corresponds to a negligible number of preparatory courses for higher education in Denmark and was therefore not included.

Applying generally accepted criteria and knowledge, SCD was defined as the sudden, natural (ie, was not caused by suicide or accident), and unexpected death of cardiac or unknown cause; in witnessed cases as an acute change in cardiovascular status with the time of death <1 hour, and in unwitnessed cases as a person seen alive and functioning normally <24 hours before the time of death.[3–5,31] Autopsied SCD cases were subdivided into 2 groups: (1) explained SCD, where the cardiac cause of death was established, and (2) sudden arrhythmic death syndrome (SADS), where the cause of death remained unknown after autopsy. The explained SCD group includes the following diagnoses based on autopsy findings: ischemic heart disease,

myocarditis, thoracic aortic dissection, hypertrophic heart, cardiac fibrosis, arrhythmogenic right ventricular cardiomyopathy, valve disease, other congenital heart conditions, conduction defects, dilated cardiomyopathy, pulmonary heart disease, malformation of coronary vessel, connective tissue disease, hypertrophic cardiomyopathy, coarctatio aortae, Takyasu arteritis, and endocarditis. Nonautopsied cases of SCD were presumed to be of cardiac cause on the basis of the circumstances related to the death. Both the death certificate and previous medical history were reviewed. In cases where a competing disease was the potential cause of death, the case was not considered SCD.[4,5]

Statistical Analysis

We evaluated the association between BW, SGA, and LGA and outcome SCD by estimating the absolute and relative risks. We calculated the relative risk of SCD for each BW group, with BW group 2500 to 3499 g as the reference, and the relative risk of SCD for SGA and LGA infants compared with appropriate for gestational age infants for a given week of gestation. Furthermore, we estimated the absolute and relative risks of SCD for SGA and LGA infants born at term only, hereby directly adjusting for gestational age. Because of the irregular registration of BWs during 1973 to 1978, our SGA and LGA analyses were performed on data from 1979 onward. For all BW groups, SGA infants, and LGA infants, we performed additional subgroup analyses where we adjusted for gestational age and the influence of maternal comorbidities, calculating the relative risks of SCD when excluding people with gestational age at birth <37+0 weeks, people with gestational age at birth >42+0 weeks, and people of mothers who had comorbidities at birth, respectively. For the SGA and LGA infants, we also estimated the relative risk of SCD for men; women; people from mothers who had comorbidities at birth; people from mothers aged <25, 25 to 35, and >35 years; and people of mothers with different ISCED levels to examine the effect of each subgroup on the risk estimates. Lastly, we estimated the absolute and relative risks of explained SCD and SADS for SGA and LGA infants. All risks of SCD were estimated with 95% CIs for different ages using the Aalen-Johansen estimator. This nonparametric estimator handles the presence of right censoring and left truncation because of our study design, as well as the competing risk of death from other causes.[32] Categorical data were compared using the χ^2 test. Continuous variables were compared using the general linear model ANOVA, and medians were compared using the Kruskal-Wallis test. A 2-sided $P<0.05$ was considered statistically significant.

As a supplement, we performed multivariable adjustments using Cox proportional hazard regression modeling to account for potential confounding. Adjustments were made for the covariates birth year, sex of the child, maternal age, maternal comorbidities, and maternal educational level. The BW was entered both as a categorical variable as well as using a linear tail-restricted cubic spline with 3 knots. The proportionality assumption was assessed using the cumulative score process. All data analyses were performed using the SAS software package version 9.4 and R version 3.6.1.

RESULTS

The study population comprised 2 236 755 people, of whom 390 suffered SCD (Figure 1). When applying the BW groups, the study population for the BW group analyses comprised 2 234 501 people with 389 SCD cases. The study population for SGA and LGA analysis comprised 1 786 281 people with 193 cases of SCD.

Birth Characteristics

Birth characteristics according to BW groups are listed in Table 1 (missing values are listed in Table S3). There was a female predominance in the <1500,

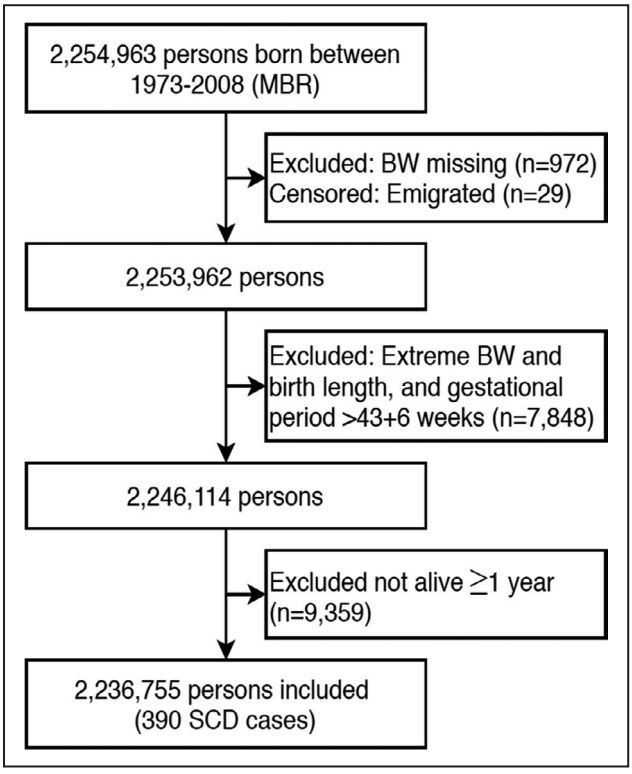

Figure 1. Flow chart depicting the selection of the study population
BW indicates birth weight; MBR, Medical Birth Register; and SCD, sudden cardiac death.

Table 1. Birth Characteristics According to Birth Weight Groups

Characteristics		<1500 g, n=17 304	1500–2499 g, n=171 256	2500–3499 g, n=1 138 356	3500–4499 g, n=857 996	≥4500 g, n=49 589
Sex	Men (%)	8465 (48.9)	78 563 (45.9)	541 434 (47.6)	483 882 (56.4)	33 565 (67.7)
	Women (%)	8839 (51.1)	92 693 (54.1)	596 922 (52.4)	374 114 (43.6)	16 024 (32.3)
Birth year	1973–1979 (%*)	6308 (1.4)	88 381 (19.3)	297 180 (64.8)	64 904 (14.2)	1522 (0.3)
	1980–1989 (%*)	3089 (0.5)	27 775 (5)	282 370 (52)	222 215 (40.5)	10 346 (2)
	1990–1999 (%*)	4154 (0.6)	29 486 (4.5)	305 490 (46.4)	299 707 (45.5)	19 060 (3)
	2000–2008 (%*)	3744 (0.6)	25 614 (4.5)	253 316 (44.3)	271 170 (47.4)	18 661 (3.2)
Birth length, cm, mean (SD)		40.6 (3.8)	47.8 (2.5)	51.1 (1.8)	53.3 (1.7)	55.8 (1.8)
Apgar score 5 min, mean (SD)		9.0 (1.9)	9.7 (1)	9.9 (0.6)	9.9 (0.6)	9.8 (0.7)
Maternal age, y, mean (SD)		27.8 (5.5)	27 (5.2)	27.6 (5)	28.8 (4.8)	29.8 (4.7)
Previous births, mean (SD)		0.7 (1)	0.7 (0.9)	0.7 (0.9)	0.7 (0.9)	0.8 (1)
Multiple birth	Single born (%†)	9690 (0.7)	122 361 (8.5)	784 236 (54.6)	494 339 (34.5)	24 354 (1.7)
	1st of multiple (%†)	1257 (7.2)	7406 (43.7)	7810 (46)	404 (2.1)	<10 (<1)
	2nd of multiple (%†)	1378 (8)	7691 (46)	7266 (43)	<400 (<2)	<10 (<1)
	3rd of multiple (%†)	96 (30)	<400 (<60)	<400 (<8)	<400 (<1)	<10 (<1)
	4th of multiple (%†)	6 (54)	<400 (<35)	<400 (<5)	<400 (<5)	<10 (<1)
Maternal smoking, n (%)		2043 (1)	16 717 (7)	132 417 (55.5)	83 629 (35)	3502 (1.5)
Maternal educational level	ISCED 0–2 (%)	5091 (29.4)	48 260 (28.2)	309 493 (27.2)	195 162 (22.7)	10 150 (20.5)
	ISCED 3 (%)	5165 (29.8)	44 920 (26.3)	379 135 (33.3)	279 015 (38.5)	19 903 (40.1)
	ISCED 5–6 (%)	2588 (15.0)	22 129 (12.9)	216 502 (19.0)	222 756 (26.0)	14 246 (28.7)
	ISCED 7–8 (%)	611 (3.5)	4629 (2.7)	52 986 (4.7)	60 241 (7.0)	3578 (7.2)
	Unknown (%)	3849 (22.2)	51 318 (30.0)	180 240 (15.8)	48 862 (5.7)	1712 (3.5)
SCD, n (%)		<10 (<3)	65 (17)	208 (53)	105 (27)	<10 (<3)

ISCED indicates International Standard Classification of Education; and SCD, sudden cardiac death.
*Distribution in percent for each time period.
†Distribution in percent for each multiple birth category.

1500 to 2499, and 2500 to 3499 g BW group, and a male predominance in the 3500 to 4499 g and ≥4500 g BW group. Older maternal age increased the probability of higher BW in offspring. Overall, maternal smoking decreased with increased BW. Lower BW in offspring was associated with lower maternal ISCED level; however, the percentage of unknown educational status was considerably higher for mothers in the BW groups <1500 g and 1500 to 2499 g compared with the BW groups 3500 to 4499 g and ≥4500 g. Birth characteristics according to size for gestational age are listed in Table 2 (missing values are listed in Table S4). There was a female predominance within the SGA infants and a male predominance within both the appropriate for gestational age and LGA infants. An increase in maternal age was associated with an increase in the size of the infant. Maternal smoking was higher for mothers of SGA infants compared with mothers of both appropriate for gestational age and LGA infants. Size for gestational age in the infant was positively correlated to the maternal ISCED level.

Risk of SCD in the Young

The absolute risk of SCD for the BW groups is illustrated in Figure 2. The age-specific relative risks of SCD are presented in Table 3. The relative risk of SCD at age 5 years was 6.69 for people with BW between 1500 and 2499 g (95% CI, 2.38–18.80, $P<0.001$) and 5.89 if BW was ≥4500 g (95% CI, 1.81–19.12, $P=0.003$). Furthermore, the relative risk of SCD at age 15 years was 4.26 for people with BW between 1500 and 2499 g (95% CI, 2.04–8.92, $P<0.001$) and 2.96 if BW was ≥4500 g (95% CI, 1.13–7.76, $P=0.028$). The relative risk of SCD at age 30 years for people with BW between 1500 and 2499 g was 1.65 (95% CI, 1.13–2.41, $P=0.010$) and 1.60 (95% CI, 0.65–3.91, $P=0.305$) for people with BW ≥4500 g. When excluding people with gestational age at birth <37+0 weeks, people with gestational age at birth >42+0 weeks, and people of mothers who had

Table 2. Birth Characteristics According to Size for Gestational Age

Characteristics		SGA, n=171 355	AGA, n=1 446 889	LGA, n=168 037
Sex	Men (%)	68 110 (39.7)	739 697 (51.1)	108 397 (64.5)
	Women (%)	103 245 (60.3)	707 192 (48.9)	59 640 (35.5)
Birth year	1979 (%*)	5458 (12.6)	34 982 (81)	2777 (6.4)
	1980–1989 (%*)	61 119 (11.6)	426 222 (81.1)	38 754 (7.3)
	1990–1999 (%*)	58 103 (9)	521 650 (80.6)	66 912 (10.4)
	2000–2008 (%*)	46 675 (8.2)	464 035 (81.4)	59 594 (10.4)
Birth length, cm, mean (SD)		48.9 (2.6)	51.7 (2.4)	54.4 (2.2)
Apgar score 5 min, mean (SD)		9.8 (0.8)	9.9 (0.6)	9.8 (0.7)
Maternal age, y, mean (SD)		27.9 (5.1)	28.5 (4.9)	29.6 (4.8)
Previous births, mean (SD)		0.6 (0.9)	0.7 (0.9)	0.8 (1)
Multiple birth	Single born (%†)	100 315 (10)	814 336 (81.1)	88 974 (8.9)
	1st of multiple (%†)	3328 (25)	9414 (73)	<200 (<2)
	2nd of multiple (%†)	3921 (31)	8660 (67)	<200 (<2)
	3rd of multiple (%†)	<200 (<31)	178 (68)	<200 (<1)
	4th of multiple (%†)	<200 (<12)	7 (87)	<200 (<1)
Maternal smoking, n (%)		34 022 (14.5)	188 579 (79.5)	14 334 (6)
Maternal educational level	ISCED 0–2 (%)	59 286 (34.6)	373 122 (25.8)	36 557 (21.8)
	ISCED 3 (%)	65 195 (38)	569 057 (39.3)	67 899 (40.4)
	ISCED 5–6 (%)	32 167 (18.8)	356 142 (24.6)	46 470 (27.7)
	ISCED 7–8 (%)	7996 (4.7)	97 028 (6.7)	11 917 (7.1)
	Unknown (%)	6711 (3.9)	51 540 (3.6)	5194 (3.1)
SCD, n (%)		31 (16.1)	143 (74.1)	19 (9.8)

AGA indicates appropriate for gestational age; ISCED, international standard classification of education; LGA, large for gestational age; SCD, sudden cardiac death; and SGA, small for gestational age.

*Distribution in percent for each time period.

†Distribution in percent for each multiple birth category.

comorbidities at birth, the increased relative risk at all ages remained for people with BW between 1500 and 2499 g and at age 5 years only for people with BW ≥4500 g (Table S5). The BW group of 2500 to 3499 g was the reference for all estimates. The absolute risk of SCD among SGA and LGA infants is illustrated in Figure 3A. The age-specific relative risks of SCD are presented in Table 4. For SGA infants, the relative risk was 2.85 at age 10 years (95% CI, 1.35–6.00, *P*=0.006), 2.35 at age 15 years (95% CI, 1.25–4.43, *P*=0.008), 1.97 at age 20 years (95% CI, 1.21–3.21, *P*=0.006), and 1.75 at age 25 years (95% CI, 1.16–2.36, *P*=0.007). There were no significant increased relative risks of SCD for LGA infants. For the subgroup analyses, the increased relative risk of SCD for SGA infants remained after excluding people with gestational age at birth <37+0 weeks, excluding people with gestational age at birth >42+0 weeks, and excluding people of mothers who had comorbidities at birth, at age 10, 15, 20, and 25 years. Furthermore, there were some increased relative risks of SCD for female SGA infants, SGA infants of mothers aged <25 years, and SGA infants of mothers in ISCED level 0 to 2 and level 3 (Table S6). The absolute risks of SCD for SGA and LGA infants born at term are illustrated in Figure 3B, and the age-specific relative risks are presented in Table 4. The relative risk of SCD for SGA infants born at term was 2.64 at age 10 years (95% CI, 1.21–5.77, *P*=0.015), 2.16 at age 15 years (95% CI, 1.08–4.31, *P*=0.028), 1.79 at age 20 years (95% CI, 1.06–3.02, *P*=0.030), and 1.66 at age 25 years (95% CI, 1.08–2.55, *P*=0.020). There were no significant increased relative risks of SCD for LGA infants born at term.

Finally, Cox regression revealed no indication of important confounding. We found no notable difference between crude hazard ratios and multivariable hazard ratios (Figure S1).

Cause of Death in Autopsied SCD Cases

The absolute risks of SADS and explained SCD for SGA and LGA infants are illustrated in Figure 4A and 4B, and the relative risks are presented in Tables 5 and 6. The relative risk of SADS for SGA infants was 4.19 at age 5 years (95% CI, 1.08–16.22, *P*=0.038), 4.21 at age 15 years (95% CI, 1.46–12.14, *P*=0.008), and 2.22 at age 30 years (95% CI, 1.05–4.69, *P*=0.036). We found similar results when estimating the relative risks for SGA infants born at term. There were no significant increased relative risks of SADS among LGA infants. We found no association between SGA or LGA and risk of explained SCD.

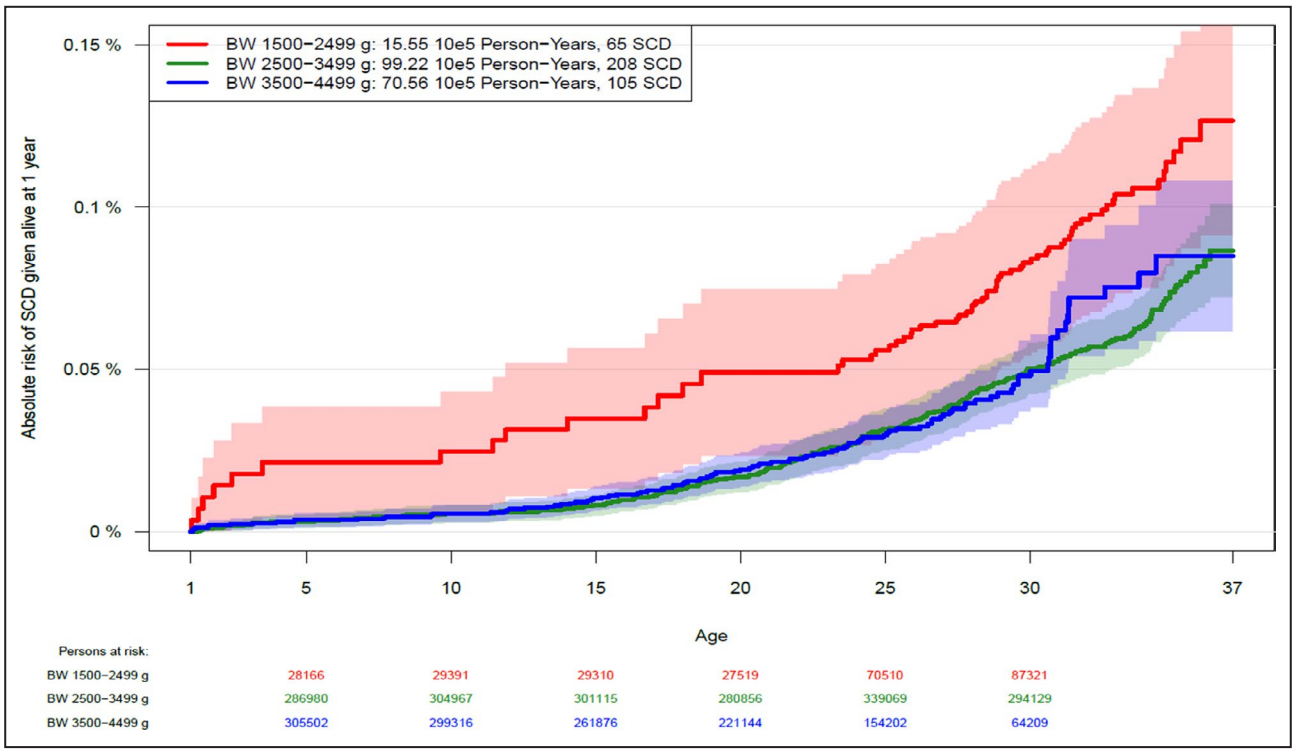

Figure 2. Absolute risk of sudden cardiac death (SCD) per birth weight (BW) group.
BW group <1500 and ≥4500 g not shown because there were too few cases.

DISCUSSION

In this Danish nationwide study, we investigated and found an association between BW and SCD in the young (aged 1–36 years). We adjusted for the influence of gestational age and found an association between SGA and SCD as well. Moreover, we found an association between SGA and SADS among autopsied cases.

Risk of SCD in the Young

We found an association between BW and the risk of SCD, with the highest relative risk of SCD among infants with BW between 1500 and 2499 g and BW ≥4500 g, and risk decreasing with increasing age of the child for both BW groups. We were not able to estimate the relative risk of SCD for people with BW <1500 g at all ages because there were too few cases. The absolute risk of death of other causes was highest among infants with BW <1500 g (data not shown). Although we attempted to reduce the possible influence of comorbidities and complications in relation to low BW and prematurity by estimating risks for those alive at 1 year of age, conditions associated with low BW may account for these findings. Studies have suggested that growth restriction during pregnancy resulting in SGA infants is associated with cardiovascular programming and remodeling, with long-term cardiovascular consequences.[33] We found an increased relative risk of SCD among SGA infants, with similar trends remaining after direct adjustment for gestational age. Furthermore, we wanted to investigate whether there is an association between LGA and risk of SCD, because there has

Table 3. Age-Specific Relative Risk [95% CI] of Sudden Cardiac Death for Birth Weight Groups

Age, y	<1500 g	1500–2499 g	3500–4499 g	≥4500 g
5	NA	6.69 [2.38–18.80], *P*<0.001	1.14 [0.47–2.74], *P*=0.775	5.89 [1.81–19.12], *P*=0.003
10	NA	4.46 [1.83–10.84], *P*=0.001	1.01 [0.51–2.00], *P*=0.982	3.39 [1.13–10.13], *P*=0.029
15	NA	4.26 [2.04–8.92], *P*<0.001	1.26 [0.74–2.15], *P*=0.401	2.96 [1.13–7.76], *P*=0.028
20	NA	2.92 [1.61–5.29], *P*<0.001	1.14 [0.77–1.69], *P*=0.510	1.44 [0.57–3.61], *P*=0.440
25	0.65 [0.09–4.69], *P*=0.672	1.77 [1.06–2.97], *P*=0.030	0.94 [0.69–1.29], *P*=0.706	1.66 [0.69–4.00], *P*=0.262
30	0.69 [0.17–2.86], *P*=0.614	1.65 [1.13–2.41], *P*=0.010	0.95 [0.73–1.26], *P*=0.740	1.60 [0.65–3.91], *P*=0.305

P value refers to the difference compared with birth weight group 2500–3499 g. NA indicates not available because there were too few cases.

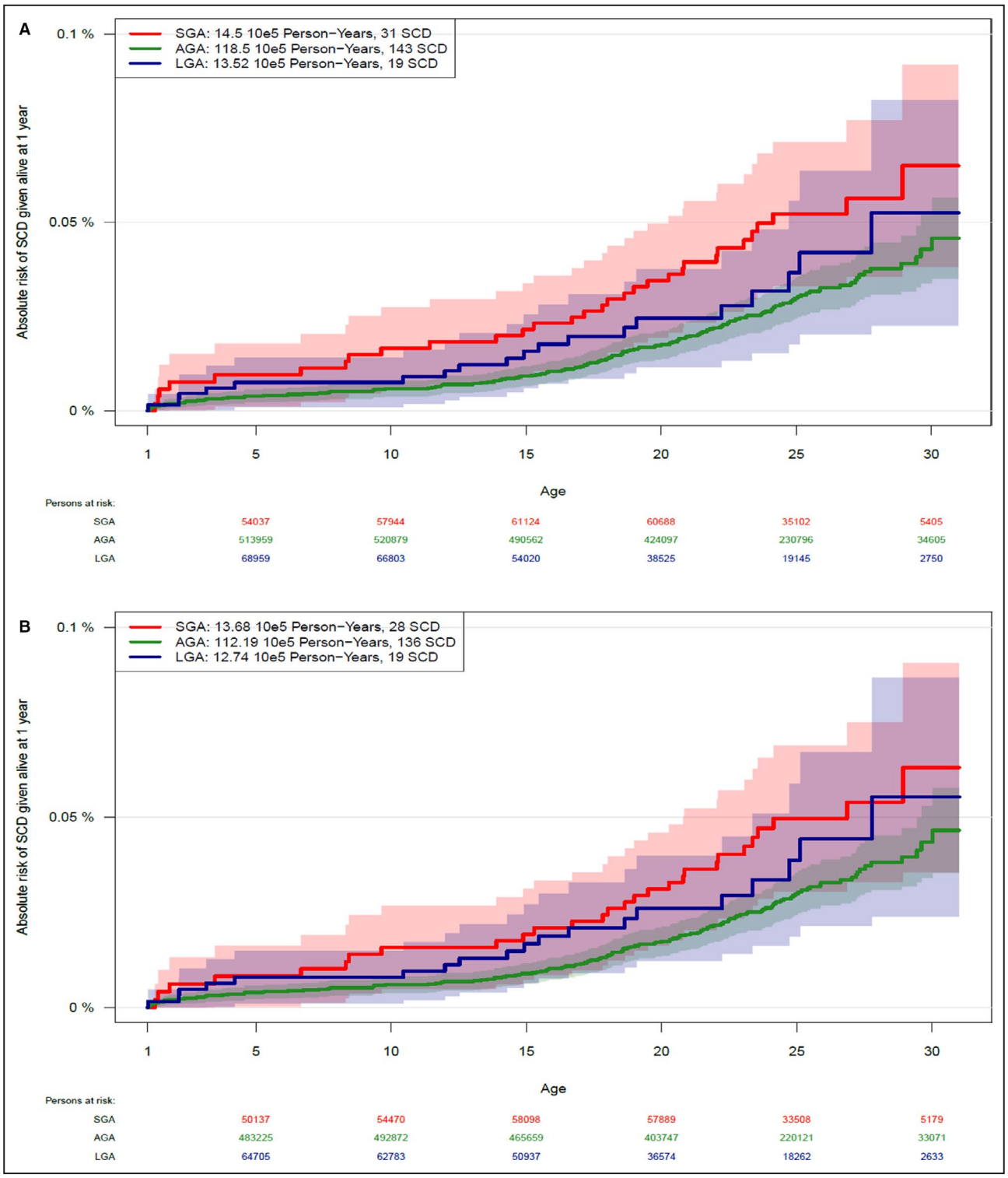

Figure 3. Absolute risk of sudden cardiac death (SCD) per size for gestational age (A) and absolute risk of SCD per size for gestational age born at term (B).
AGA indicates appropriate for gestational age; LGA, large for gestational age; and SGA, small for gestational age.

been an increase in mean BW in Denmark over the past 30 years, and macrosomia (excessive BW) and LGA are closely related to the risk of fetal and maternal complications in relation to birth.[34,35] Our results showed a nonsignificant increased relative risk of SCD among LGA infants. The relative risk of SCD remained increased for people with BW between 1500 and 2499 g and SGA people after adjusting

Table 4. Age-Specific Relative Risk [95% CI] of Sudden Cardiac Death for SGA and LGA Infants and SGA and LGA Infants Born at Term

Age, y	SGA	LGA	SGA at Term	LGA at Term
5	2.44 [0.91–6.49], *P*=0.075	1.92 [0.72–5.11], *P*=0.193	2.08 [0.71–6.12], *P*=0.183	2.01 [0.75–5.39], *P*=0.164
10	2.85 [1.35–6.00], *P*=0.006	1.29 [0.50–3.31], *P*=0.604	2.64 [1.21–5.77], *P*=0.015	1.33 [0.51–3.43], *P*=0.557
15	2.35 [1.25–4.43], *P*=0.008	1.72 [0.87–3.40], *P*=0.122	2.16 [1.08–4.31], *P*=0.028	1.88 [0.94–3.74], *P*=0.073
20	1.97 [1.21–3.21], *P*=0.006	1.40 [0.79–2.49], *P*=0.247	1.79 [1.06–3.02], *P*=0.030	1.49 [0.84–2.66], *P*=0.172
25	1.75 [1.16–2.63], *P*=0.007	1.23 [0.71–2.13], *P*=0.465	1.66 [1.08–2.55], *P*=0.020	1.30 [0.75–2.25], *P*=0.356
30	1.52 [0.95–2.41], *P*=0.079	1.22 [0.67–2.25], *P*=0.514	1.45 [0.89–2.36], *P*=0.136	1.27 [0.69–2.34], *P*=0.440

P value refers to the difference compared with appropriate for gestational age. LGA indicates large for gestational age; and SGA, small for gestational age.

for prematurity, prolonged pregnancies, and maternal comorbidities. These findings strengthen the relationship discovered between BW and SCD, because the risks of SCD remained increased when we excluded factors potentially influencing the association. Our results may hereby underpin the fetal origins of the adult disease hypothesis, as environmental factors that impair the intrauterine development of the heart may be possible risk factors for SCD later in life.

Other Factors Influencing BW

In line with other Nordic studies, we used the mother's highest completed educational level as a measurement of socioeconomic status, because it has been reported that there is a clear association between low parental educational level and low BW and SGA, with maternal educational level having the strongest influence.[36] We included the mother's highest completed educational level when the child was 5 years old for our analyses, thereby attempting to avoid the possible bias of higher-educated women giving birth while in school. Our results are in accordance with other studies, because lower maternal educational level was associated with lower BW and SGA in offspring.[36] Maternal smoking is an important mediating factor of socioeconomic status in infant growth restriction and should be taken into consideration when evaluating the influence of socioeconomic status.[37] In our study population, the proportion of smoking mothers abated with increasing ISCED level, coinciding with previous studies (data not shown).[38] Additionally, our results showed a positive correlation between maternal age and BW, which also is aligned with previous results.[39] Moreover, during the past decades in Denmark, a growing proportion of highly educated women have postponed their first pregnancy.[40] The association between maternal educational level and BW in offspring may therefore be related to the lower proportion of maternal smoking among highly educated women and the inclination of higher-educated women getting pregnant at an older age, in addition to other lifestyle factors such as nutrition and exercise associated with higher education.

Overall, our results showed an association between the sex of the child, maternal age, and maternal educational status and the BW in offspring. When adjusting for these factors, we found an increased relative risk of SCD among female SGA infants, SGA infants of younger mothers, and SGA infants of mothers with lower socioeconomic status. These results may imply that the sex of the child, lower maternal age, and socioeconomic status increase the risk of giving birth to a child who will suffer SCD; however, because of a lack of statistical power, we believe a larger sample size is necessary to investigate this further. Thus, the influence of these factors on the risk of SCD was not adequately elucidated on the basis of our findings.

Cause of Death in Autopsied SCD Cases

The distribution of explained SCD and SADS in the younger Danish population has previously been described, and we wanted to explore whether explained SCD or SADS was more prominent among SGA and LGA infants.[4] Our findings showed a clear signal with greater risk of SADS among SGA infants, and similar results were obtained when directly adjusting for gestational age. Primary arrhythmogenic disorders because of underlying genetic defects constitute an important cause of sudden death in the young, because approximately 30% of SADS cases have a clinically relevant gene mutation causing cardiac channelopathies.[41] A recent study described the clinical utility of the identification of the genetic variants in SADS and how these results, combined with a clinical and genetic evaluation of surviving relatives, can enhance the diagnostic value.[42] On the basis of our findings, one may hypothesize that fetal arrhythmia or other conditions in the fetus caused by genetic mutations can impair fetal growth. However, these results may also indicate that conditions during pregnancy can impair the development of the heart with formation of electrical abnormalities. Thus, our results call for further investigation because it may add to the identification of people at risk of SADS.

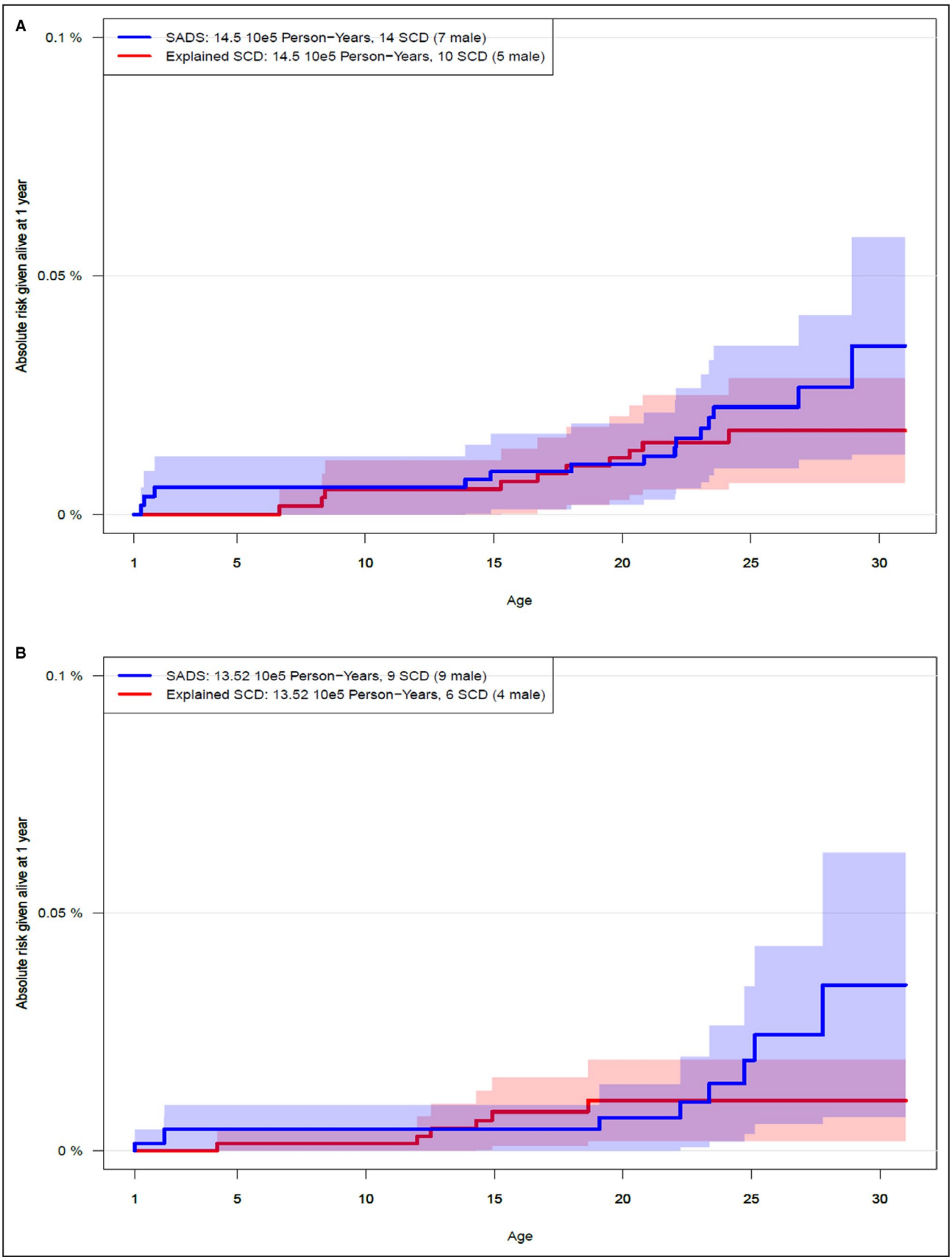

Figure 4. Absolute risk of sudden arrhythmic death syndrome (SADS) and explained sudden cardiac death (SCD) among small for gestational age (A) and absolute risk of SADS and explained SCD among large for gestational age (B).

Table 5. Age-Specific Relative Risk [95% CI] of Sudden Arrhythmic Death Syndrome for SGA and LGA Infants and SGA and LGA Infants Born at Term

Age, y	SGA	LGA	SGA at Term	LGA at Term
5	4.19 [1.08–16.22], *P*=0.038	3.31 [0.86–12.80], *P*=0.083	4.26 [1.10–16.47], *P*=0.036	3.30 [0.85–12.75], *P*=0.084
10	2.95 [0.81–10.72], *P*=0.100	2.33 [0.64–8.46], *P*=0.199	3.00 [0.83–10.92], *P*=0.095	2.32 [0.64–8.45], *P*=0.200
15	4.21 [1.46–12.14], *P*=0.008	2.11 [0.59–7.57], *P*=0.251	4.25 [1.47–12.26], *P*=0.007	2.11 [0.59–7.57], *P*=0.251
20	2.03 [0.83–4.96], *P*=0.121	1.33 [0.45–3.92], *P*=0.605	2.05 [0.84–5.02], *P*=0.115	1.34 [0.45–3.93], *P*=0.600
25	2.29 [1.20–4.38], *P*=0.013	1.93 [0.81–4.64], *P*=0.139	2.42 [1.26–4.65], *P*=0.008	2.03 [0.85–4.88], *P*=0.112
30	2.22 [1.05–4.69], *P*=0.036	2.20 [0.91–5.30], *P*=0.080	2.30 [1.09–4.86], *P*=0.029	2.26 [0.94–5.48], *P*=0.070

P value refers to the difference compared with appropriate for gestational age. LGA indicates large for gestational age; and SGA, small for gestational age.

Other Risk Factors of SCD in the Young

There are other reports describing risk factors of SCD based on the similar SCD population used for this study.[4,5] Within the young, most people suffering SCD caused by coronary artery disease have had symptoms before death, and prior psychiatric hospital contact has been associated with a substantially higher risk of SCD.[43,44] Younger people with epilepsy have an increased hazard ratio of premature death and sudden unexplained death compared with people without epilepsy.[45] Diabetes mellitus has been associated with considerably higher SCD incidence rates among the young compared with people without diabetes mellitus.[46] Another study has described an increase in the frequency of febrile seizures before death in young SCD cases compared with both a living and dead control group, with SADS being the most common cause of death among autopsied SCD cases with febrile seizures.[47] Pharmacotherapy was previously identified in 58% of the young SCD cases, and certain drugs (eg, brugadogenic drugs and QT-prolonging drugs) were associated with an increased risk of SADS compared with explained SCD.[48] In relation to these documented risk factors, our findings can contribute to the development of preventative initiatives in the future such as risk prediction models for SCD in the young.

Strengths and Limitations

We used highly validated registers for this study. As previously mentioned, the accuracy of BW registered in the MBR varies over time. Because of the irregular registration during 1973 to 1978, SGA and LGA analyses were performed on data from 1979 and onward, with 193 SCD cases compared with 389 SCD cases for the BW analyses. Immigrants were not included, because BW is not registered in the MBR for people born abroad. Apart from maternal smoking, there was no self-reported information, hereby avoiding recall bias. The amount of smoking pregnant women could be biased when reporting because of an increase in public awareness of the adverse effects of smoking during pregnancy. We were not able to adjust for the possible influence of maternal smoking on the association between BW and size for gestational age and risk of SCD because there were too few cases, which must be considered as a limitation. The SCD subgroup analyses were performed on only autopsied SCD cases. The autopsy rate for SCD cases during 2000 to 2009 was ≈75%, which should be considered as a cause for selection bias when interpreting these findings.[4,5]

CONCLUSIONS

We found a relationship between BW and risk of SCD, with an increased risk of SCD among SGA infants. Additionally, we found an association between SGA and SADS. Our results point toward the influence of early development in SCD in children, which may conceivably be linked to genetic mutations. These results may contribute to developing strategies for preventing

Table 6. Age-Specific Relative Risk [95% CI] of Explained Sudden Cardiac Death for SGA and LGA Infants and SGA and LGA Infants Born at Term

Age, y	SGA	LGA	SGA at Term	LGA at Term
5	NA	0.94 [0.12–7.52], *P*=0.954	NA	1.07 [0.13–8.73], *P*=0.946
10	2.12 [0.60–7.44], *P*=0.241	0.58 [0.08–4.45], *P*=0.603	2.31 [0.65–8.19], *P*=0.194	0.63 [0.08–4.86], *P*=0.660
15	1.09 [0.33–3.62], *P*=0.883	1.68 [0.64–4.40], *P*=0.290	1.26 [0.38–4.20], *P*=0.711	1.92 [0.72–5.07], *P*=0.190
20	1.41 [0.63–3.14], *P*=0.402	1.26 [0.53–3.00], *P*=0.600	1.56 [0.70–3.51], *P*=0.279	1.40 [0.59–3.35], *P*=0.449
25	1.51 [0.76–2.98], *P*=0.241	0.91 [0.38–2.14], *P*=0.822	1.62 [0.81–3.22], *P*=0.171	0.98 [0.41–2.32], *P*=0.962
30	1.04 [0.51–2.12], *P*=0.918	0.63 [0.26–1.51], *P*=0.297	1.09 [0.53–2.25], *P*=0.808	0.66 [0.27–1.61], *P*=0.362

P value refers to the difference compared with appropriate for gestational age. LGA indicates large for gestational age; NA, not available because there were too few cases; and SGA, small for gestational age.

SCD in the future, because BW and size for gestational age might predict the risk of SCD later in life. The present findings call for further investigation to elucidate the underlying pathophysiology.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S6
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Comorbidity ICD codes.

Comorbidity	ICD-8 code(s)	ICD-10 code(s)
Diabetes mellitus including gestational diabetes	250, 7611	E10-E14, O244
Hypertension	400, 404	I10-I15, I109, I150, I159, O139
Renal disease	403-404, 581-584, 25002, 40039, 59009, 59320, 75310, 75311, 75319	E102, E112, E132, E142, I120, N02-N08, N11, N12, N14, N18-N19, N26, N158-N160, N162-N164, N168, M300, M313, M319, Q612-Q613, Q619
Chronic heart failure	42709-42711, 42719, 42899, 78249	I50, I110, I130, I132
Thyroid disease	242, 244-245, 2420-2422, 2451, 2459	E03, E05-E06, E038-E039, E051-E053, E058-E063, E065, E069
Intestinal disease (malabsorption, Crohn's disease, ulcerative colitis, coeliac disease)	561, 563, 2691, 5631	K50-K51, K500-K501, K508-K509, K515, K518, K900, K904, K908-K909
Thrombophilia or systemic lupus erythematosus (SLE)		M32, D685-D686, M321, M329
Infection (rubella, cytomegalovirus, toxoplasmosis, syphilis)	7610, 7613-7614	O353, O988
Disease developed in relation to pregnancy	630, 635- 636, 6351, 7620, 7631	O89-O99, O980-O987, O989, O990-O998
Preeclampsia	6370	O11, O14, O140-O141, O149

ICD-8: International Classification of Diseases, 8th revision. ICD-10: International Classification of Diseases, 10th revision.

Table S2. ATC classification codes.

Pharmacotherapy	ATC code(s)
Beta-blockers	C07, C09BX
Calcium channel blockers	C07F, C08, C09BB, C09DB
Renin-angiotensin-system inhibitors	C09
Vasodilator drugs	C02DB, C02DD, C02DG
Antiadrenergic drugs	C02A, C02B, C02C
Thiazides	C03A, C07B, C07D, C03EA01
Loop diuretics	C03C, C03EB01, C03EB02
Mineralocorticoid receptor antagonists	C03DA01, C03DA02, C03DA03, C03DA04
Anti-diabetics	A10
Diuretics combined with other drugs	C07C, C08G, C03B, C09BA, C09DA

ATC: Anatomical Therapeutic Chemical.

Table S3. Number of missing observations according to BW groups.

Characteristics	<1500 g (n=17304)	1500-2499 g (n=171256)	2500-3499 g (n=1138356)	3500-4499 g (n=857996)	≥4500 g (n=49589)
Birth Length, cm	2323	4095	5047	3493	317
Apgar Score 5 min	5825	74356	231060	39177	795
Number of Previous Births	3012	19482	171585	144628	7462
Multiple Birth	4877	33605	339024	362928	25229
Maternal Smoking	11000	125141	666987	370731	17258

BW: birth weight.

Table S4. Number of missing observations according to size for gestational age.

Characteristics	SGA (n=171355)	AGA (n=1446889)	LGA (n=168037)
Birth Length, cm	2534	10299	1226
Apgar Score 5 min	1414	7894	884
Number of Previous Births	37178	279921	23924
Multiple Birth	63707	614294	78710
Maternal Smoking	83961	604929	58842

SGA: small for gestational age. AGA: appropriate for gestational age. LGA: large for gestational age.

Table S5. Age-specific relative risk [95% confidence interval] of SCD for BW groups within subgroups.

Subgroup	Age in years	<1500 g	1500-2499 g	3500-4499 g	≥4500 g
No gestation <37+0 weeks	5	/	11.46 [3.53-37.21], p<0.001	1.07 [0.44-2.58], p=0.879	5.54 [1.71-18.00], p=0.004
	10	/	7.93 [2.90-21.70], p<0.001	0.95 [0.48-1.89], p=0.889	3.19 [1.07-9.54], p=0.038
	15	/	5.65 [2.14-14.90], p<0.001	1.25 [0.72-2.15], p=0.428	2.93 [1.11-7.71], p=0.030
	20	/	4.06 [1.90-8.63], p<0.001	1.14 [0.77-1.70], p=0.517	1.44 [0.57-3.62], p=0.441
	25	/	2.55 [1.32-4.93], p=0.005	0.98 [0.71-1.35], p=0.888	1.79 [0.73-4.41], p=0.207
	30	1.89 [0.26-13.51], p=0.525	2.05 [1.21-3.49], p=0.008	1.05 [0.79-1.40], p=0.722	1.14 [0.47-2.78], p=0.777
No gestation >42+0 weeks	5	/	6.55 [2.33-18.39], p<0.001	0.97 [0.38-2.44], p=0.947	6.58 [2.03-21.36], p=0.002
	10	/	4.37 [1.80-10.63], p=0.001	0.92 [0.46-1.86], p=0.818	3.79 [1.27-11.34], p=0.017
	15	/	4.20 [2.01-8.79], p<0.001	1.16 [0.67-2.01], p=0.595	2.59 [0.90-7.46], p=0.078
	20	/	2.89 [1.59-5.23], p<0.001	1.10 [0.74-1.64], p=0.640	1.26 [0.46-3.50], p=0.651
	25	0.65 [0.09-4.65], p=0.666	1.76 [1.05-2.95], p=0.032	0.92 [0.67-1.27], p=0.620	1.21 [0.43-3.42], p=0.725
	30	0.69 [0.17-2.86], p=0.613	1.65 [1.13-2.41], p=0.010	0.95 [0.72-1.25], p=0.716	1.33 [0.47-3.73], p=0.589
No maternal comorbidities	5	/	7.68 [2.66-22.12], p<0.001	1.16 [0.46-2.95], p=0.751	5.02 [1.33-18.91], p=0.017
	10	/	5.19 [2.09-12.85], p<0.001	1.08 [0.53-2.22], p=0.824	2.91 [0.84-10.13], p=0.093
	15	/	4.75 [2.25-10.04], p<0.001	1.34 [0.77-2.34], p=0.299	2.61 [0.90-7.61], p=0.078
	20	/	3.24 [1.78-5.90], p<0.001	1.14 [0.76-1.72], p=0.522	1.25 [0.45-3.48], p=0.674
	25	0.71 [0.10-5.08], p=0.731	1.92 [1.14-3.23], p=0.014	0.94 [0.68-1.30], p=0.712	1.24 [0.42-3.69], p=0.695
	30	0.74 [0.18-3.06], p=0.676	1.71 [1.16-2.53], p=0.007	0.96 [0.72-1.28], p=0.787	1.40 [0.48-4.05], p=0.536

SCD: sudden cardiac death. BW: birth weight. /: Not available due to too few cases. P-value refers to the difference compared to BW group 2500-3499 g.

Table S6. Age-specific relative risk [95% confidence interval] of SCD for SGA and LGA infants within subgroups.

Subgroup	Age in years	SGA	LGA
No gestation <37+0 weeks	5	2.08 [0.71-6.11], p=0.183	2.02 [0.76-5.42], p=0.161
	10	2.63 [1.20-5.77], p=0.015	1.33 [0.52-3.45], p=0.551
	15	2.16 [1.08-4.30], p=0.029	1.89 [0.95-3.76], p=0.071
	20	1.78 [1.06-3.02], p=0.031	1.50 [0.84-2.67], p=0.166
	25	1.66 [1.08-2.55], p=0.020	1.30 [0.75-2.26], p=0.346
	30	1.45 [0.89-2.36], p=0.137	1.28 [0.70-2.35], p=0.429
No gestation >42+0 weeks	5	2.69 [1.00-7.25], p=0.050	2.14 [0.80-5.77], p=0.132
	10	3.03 [1.43-6.43], p=0.004	1.39 [0.54-3.60], p=0.496
	15	2.51 [1.32-4.75], p=0.005	1.66 [0.81-3.40], p=0.167
	20	2.04 [1.25-3.34], p=0.004	1.36 [0.75-2.47], p=0.303
	25	1.79 [1.19-2.69], p=0.005	1.09 [0.61-1.95], p=0.769
	30	1.54 [0.97-2.45], p=0.067	1.13 [0.59-2.15], p=0.712
No maternal comorbidities	5	2.70 [1.00-7.26], p=0.050	1.68 [0.57-4.97], p=0.346
	10	2.72 [1.24-5.97], p=0.013	1.08 [0.38-3.08], p=0.884
	15	2.24 [1.16-4.33], p=0.017	1.62 [0.79-3.31], p=0.191
	20	2.03 [1.23-3.36], p=0.006	1.43 [0.79-2.60], p=0.239
	25	1.81 [1.19-2.74], p=0.006	1.00 [0.55-1.82], p=0.990
	30	1.58 [0.98-2.54], p=0.062	1.08 [0.55-2.14], p=0.815
Maternal comorbidities	5	/	3.26 [0.30-35.95], p=0.334
	10	2.52 [0.23-27.76], p=0.451	3.26 [0.30-35.95], p=0.334
	15	2.52 [0.23-27.76], p=0.451	3.26 [0.30-35.95], p=0.334
	20	1.36 [0.16-11.49], p=0.779	1.76 [0.21-14.88], p=0.604
	25	1.07 [0.13-8.67], p=0.950	3.51 [0.90-13.67], p=0.070
	30	0.80 [0.10-6.34], p=0.836	2.64 [0.71-9.85], p=0.148
Male	5	2.07 [0.59-7.20], p=0.253	2.11 [0.69-6.40], p=0.189
	10	1.82 [0.63-5.31], p=0.271	1.41 [0.48-4.11], p=0.528
	15	1.37 [0.53-3.50], p=0.512	1.09 [0.43-2.78], p=0.859
	20	1.25 [0.62-2.53], p=0.526	0.94 [0.42-2.10], p=0.883
	25	1.37 [0.77-2.43], p=0.279	1.20 [0.58-2.46], p=0.623
	30	0.85 [0.47-1.54], p=0.603	1.23 [0.58-2.62], p=0.593
Female	5	3.23 [0.65-16.01], p=0.151	1.21 [0.15-10.07], p=0.859
	10	5.15 [1.72-15.37], p=0.003	0.81 [0.10-6.42], p=0.844
	15	4.50 [1.81-11.15], p=0.001	2.27 [0.75-6.93], p=0.149
	20	3.30 [1.58-6.88], p=0.001	2.38 [1.02-5.54], p=0.045
	25	2.24 [1.22-4.12], p=0.009	1.16 [0.52-2.60], p=0.723
	30	3.07 [1.54-6.13], p=0.001	1.04 [0.46-2.33], p=0.933
Maternal age <25 years	5	9.83 [1.38-69.91], p=0.022	/
	10	16.62 [3.01-91.71], p=0.001	/
	15	8.55 [2.23-32.78], p=0.002	1.25 [0.15-10.85], p=0.837
	20	5.51 [2.09-14.50], p=0.001	1.20 [0.27-5.37], p=0.808
	25	2.77 [1.31-5.87], p=0.008	0.47 [0.11-1.98], p=0.306

	30	1.87 [0.89-3.92], p=0.098	0.89 [0.22-3.57], p=0.870
Maternal	5	1.22 [0.28-5.29], p=0.794	1.89 [0.63-5.65], p=0.255
25-35 years	10	1.11 [0.34-3.68], p=0.860	1.16 [0.41-3.33], p=0.781
	15	1.19 [0.47-3.01], p=0.717	1.43 [0.64-3.20], p=0.388
	20	1.29 [0.66-2.50], p=0.458	1.23 [0.62-2.41], p=0.556
	25	1.54 [0.89-2.66], p=0.120	1.23 [0.63-2.41], p=0.552
	30	1.64 [0.84-3.21], p=0.146	1.06 [0.53-2.13], p=0.875
Maternal	5	4.18 [0.38-46.15], p=0.243	4.01 [0.36-44.24], p=0.257
>35 years	10	9.58 [1.34-68.58], p=0.024	4.01 [0.36-44.24], p=0.257
	15	8.35 [1.62-43.19], p=0.011	5.13 [0.82-32.09], p=0.081
	20	3.08 [0.75-12.73], p=0.120	1.89 [0.37-9.71], p=0.446
	25	3.08 [0.75-12.73], p=0.120	5.54 [1.11-27.76], p=0.037
	30	1.95 [0.46-8.34], p=0.366	3.51 [0.68-18.12], p=0.133
Maternal	5	3.85 [0.75-19.84], p=0.107	/
ISCED 0-2	10	4.46 [1.09-18.18], p=0.037	/
	15	2.70 [0.74-9.80], p=0.131	/
	20	2.64 [1.20-5.79], p=0.016	0.80 [0.24-2.63], p=0.716
	25	2.05 [1.02-4.10], p=0.043	1.34 [0.56-3.22], p=0.514
	30	1.87 [0.89-3.91], p=0.099	1.15 [0.51-2.63], p=0.733
Maternal	5	4.75 [1.19-18.98], p=0.028	5.14 [1.45-18.21], p=0.011
ISCED 3	10	4.70 [1.76-12.55], p=0.002	2.67 [0.86-8.30], p=0.088
	15	3.72 [1.64-8.45], p=0.002	2.94 [1.24-6.97], p=0.014
	20	2.19 [1.05-4.57], p=0.037	1.93 [0.87-4.26], p=0.105
	25	2.17 [1.15-4.07], p=0.016	1.19 [0.55-2.59], p=0.660
	30	1.90 [0.95-3.81], p=0.071	1.71 [0.56-5.20], p=0.347
Maternal	5	/	1.96 [0.22-17.55], p=0.547
ISCED 5-6	10	/	1.21 [0.15-10.07], p=0.860
	15	/	1.93 [0.40-9.18], p=0.410
	20	0.98 [0.13-7.68], p=0.985	2.73 [0.72-10.35], p=0.140
	25	1.28 [0.37-4.43], p=0.697	0.96 [0.27-3.41], p=0.950
	30	0.84 [0.22-3.13], p=0.792	0.63 [0.16-2.41], p=0.498
Maternal	5	/	/
ISCED 7-8	10	/	/
	15	/	/
	20	/	/
	25	/	/
	30	/	/
Maternal	5	/	/
ISCED unknown	10	/	/
	15	3.06 [0.32-29.40], p=0.333	2.48 [0.26-23.88], p=0.431
	20	1.59 [0.19-13.18], p=0.669	1.29 [0.16-10.71], p=0.814
	25	0.81 [0.10-6.30], p=0.842	0.66 [0.09-5.11], p=0.690
	30	0.68 [0.09-5.28], p=0.715	0.55 [0.07-4.29], p=0.572

SCD: sudden cardiac death. SGA: small for gestational age. LGA: large for gestational age.

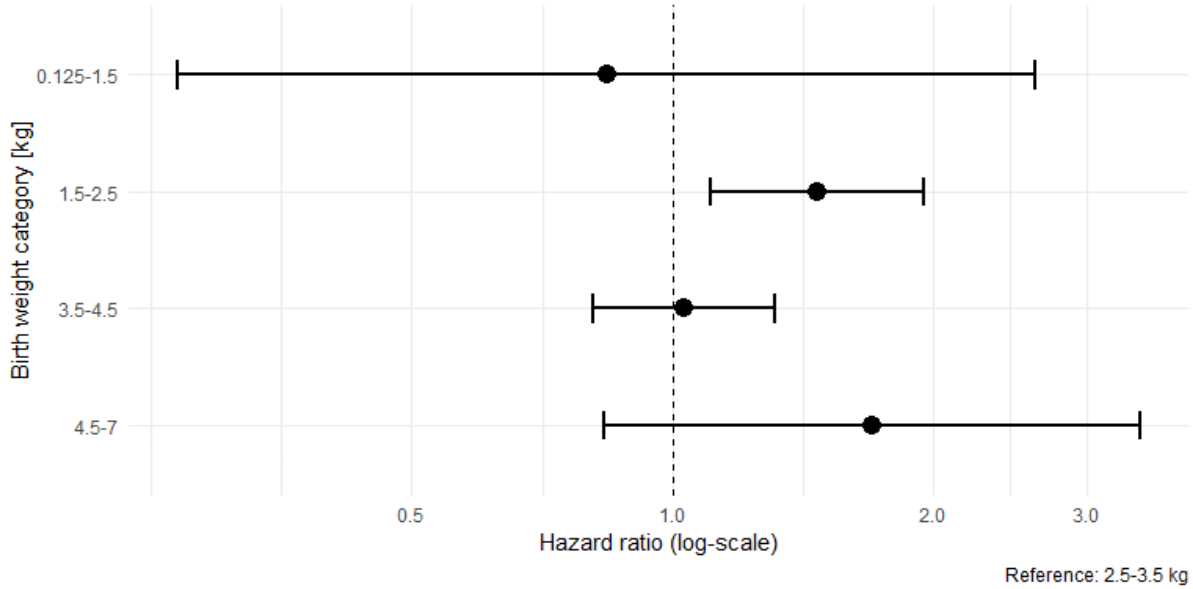
/: Not available due to too few cases. P-value refers to the difference compared to AGA (appropriate for gestational age).

Figure S1. Multivariable Adjustments

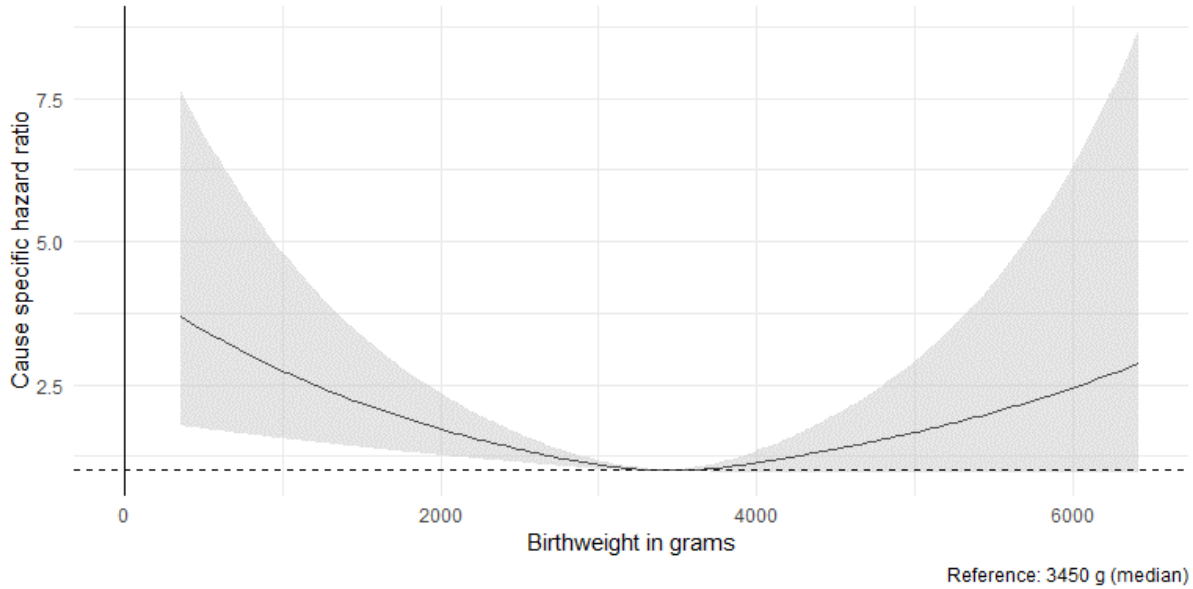
We used Cox proportional hazard regression modeling with cause-specific hazards to estimate exposure and covariates for the outcome of sudden cardiac death (SCD). In the following, we present the crude and adjusted hazard ratios (HR) of SCD with birth weight (BW) both as a categorical variable and as a continuous variable using splines.

Crude HR for BW (no adjustment)

BW as a categorical variable:

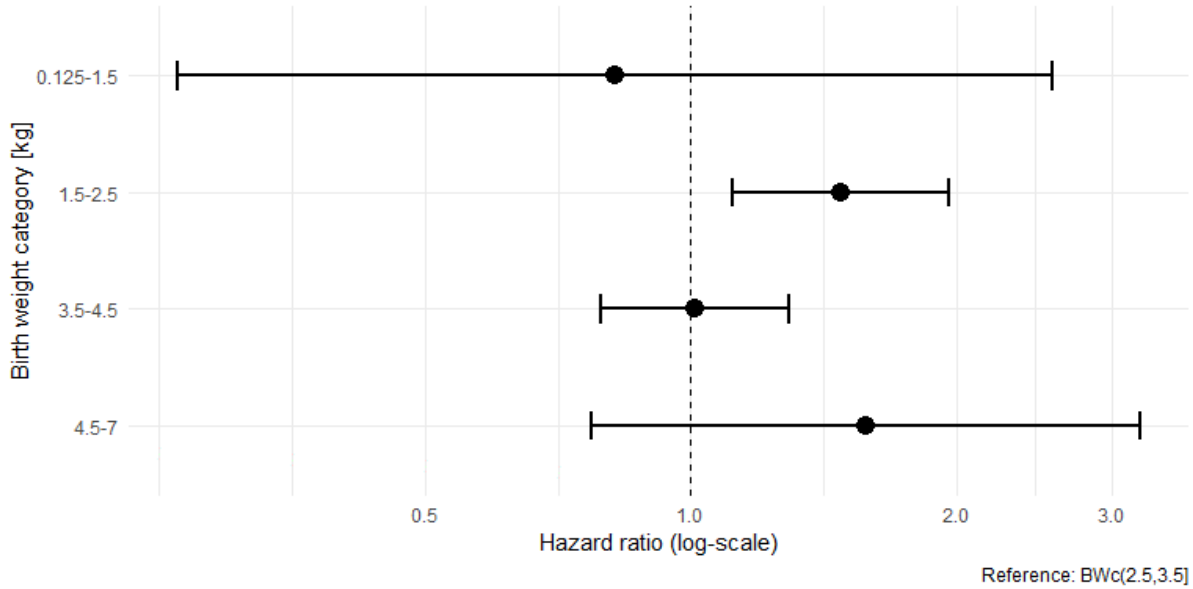


BW using a linear tail-restricted cubic spline with 3 knots:



HR for BW adjusted for sex of the child (binary), maternal age (continuous), birth year (continuous), maternal educational level (categorical) and maternal comorbidities (binary)

BW as a categorical variable:



BW using a linear tail-restricted cubic spline with 3 knots: