RESEARCH

Influence of growth and metabolic markers on hs-troponin T and NT-proBNP levels in healthy children

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Abstract

Background and objectives: As part of the LIFE Child study, we previously described the associations between *N*-terminal-pro-hormone brain natriuretic peptide (NT-proBNP) and hs-troponin T (hs-TnT) levels and an individual's sex, age and pubertal status, as well as with body mass index (BMI) and serum lipid levels. For NT-proBNP, we found inverse associations with advancing puberty, increasing BMI and serum lipid levels. These findings led us to further question the putative influences of the developing individual's metabolic and growth status as represented by levels of insulin-like growth factor-1 (IGF-1) and IGF-1-binding protein-3 (IGF-BP3) as well as hemoglobin A1c (HbA1c) and Cystatin C (CysC).
Material and methods: Serum values, medical history and anthropometric data provided by 2522 children aged 0.25–18 years were collected and analyzed as per study protocol.
Results: A strong negative association between NT-proBNP values and IGF-1, IGF-BP3 and HbA1c levels was identified. For IGF-BP3, this interaction was modulated by sex and age, for HbA1c only by age. For hs-TnT, a positive association was found with IGF-BP3, IGF-1 and CysC. The association between hs-TnT and IGF-1 was sex dependent. The association between CysC and hs-TnT was stronger in girls, but the interaction with age was only seen in boys. Between hs-TnT and HbA1c, the association was significantly negative and modulated by age.
Conclusion: Based on our large pediatric cohort, we could identify age- and sex-dependent interactions between the metabolic status represented by IGF-1, IGF-BP3, CysC and HbA1c levels and the cardiac markers NT-proBNP and hs-TnT.

Key Words
- cardiac biomarkers
- pediatric percentiles
- troponin T
- NT-proBNP
- growth factors

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Introduction

Cardiac biomarkers such as hs-troponin T (hs-TnT) and NT-proBNP are frequently used in clinical practice for the detection of acute and chronic cardiac stress. Troponin levels are established in the diagnostic work-up of suspected acute myocardial lesions such as myocardial infarction since the release is increased during myocardial injury (1). NT-proBNP levels are used in detection and follow-up of heart failure (HF) due to the increased secretion of brain natriuretic peptides as a response to atrial stretch (2). While it is known that cardiac muscle

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mass increases from birth to adolescence with a less rapid growth rate than body size (3), the influence of growth hormone factors on cardiac marker levels during normal childhood development remains not well understood.

Recent studies have investigated influences of growth hormone factors on cardiac markers in different adult cohorts and small pediatric patient groups. For example, positive correlations of IGF-BP1 and IGF-BP1/IGF-1-ratio with NT-proBNP were seen in patients with and without HF (4); in a cohort of pediatric and adult patients with Fontan physiology, higher BNP was associated with lower IGF-1 *Z* scores (5) and in 30 pediatric patients with congenital heart disease and HF, serum IGF-1 and IGF-binding protein 3 (BP3) levels were negatively correlated with serum troponin I levels (6).

As part of the prospective longitudinal population-based cohort study, 'LIFE Child' in Leipzig, Germany, we recently defined new reference values of NT-proBNP and hs-TnT obtained from healthy children. We investigated for associations between these cardiac markers and age, sex, pubertal status, body mass index (BMI) and serum lipid levels (7). Our results showed negative associations for NT-proBNP levels with advancing puberty, increasing BMI and serum lipid levels. Negative associations were also found between hs-TnT and LDL cholesterol and triglycerides in boys. Further, we found increasing hs-TnT-levels with advancing puberty from pubertal stage 2 onward in boys but not in girls, with lower levels in girls across puberty.

The aim of this subsequent study was to investigate other metabolic associations influencing NT-proBNP and hs-TnT levels. We hypothesized that associations would exist between the cardiac marker levels and an individual's growth and developmental status as represented by IGF-1 and IGFBP3 levels or their metabolic status as represented by HbA1c or the kidney function marker Cystatin C (CysC).

Materials and methods

Anthropometric data, medical and medication history together with venous blood samples were obtained at 4947 visits from 2522 children aged 0.25–18 years (49% female) participating in the prospective longitudinal population-based cohort study, LIFE Child, following standardized protocols. The study, conducted in Leipzig,

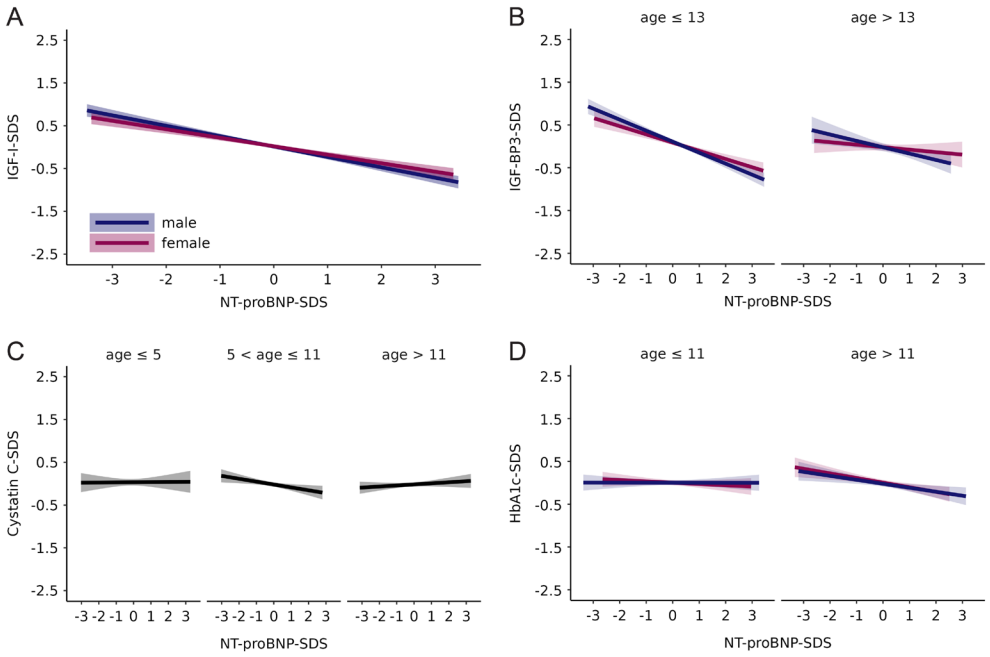

Figure 1
SDS of NT-proBNP show significant, age- and sex-dependent associations with SDS of IGF-1, IGF-BP3, Cystatin C and HbA1c. Lower NT-proBNP-SDS was associated with higher IGF-1 and IGF-BP3 levels. The latter showed a more pronounced difference between the sexes and an age dependency with a stronger association between NT-proBNP-SDS and IGF-BP3-SDS below the age of 13 years and no significant association in girls older than 13 years. NT-proBNP-SDS and HbA1c-SDS showed an inverse association with no difference between the sexes but modulated by age. The effect was stronger above 11 years and did not reach statistical significance below 11 years. For Cystatin C, we found a negative association with NT-proBNP between 5 and 11 years of age but not for children below the age of 5 years or above 11 years.

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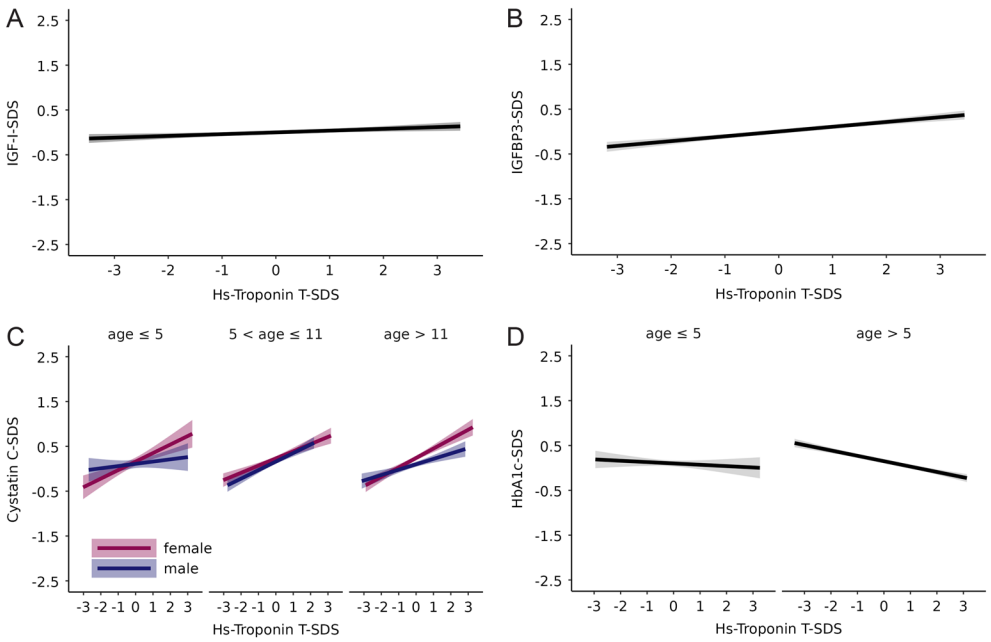

Figure 2

SDS of hs-TnT show significant, age- and sex-dependent associations with SDS of IGF-1, IGF-BP3, Cystatin C and HbA1c. We found a significant positive association between SDS of hs-TnT and IGF-1 and IGF-BP3 with the latter effect being stronger. The association between hs-TnT-SDS and HbA1c-SDS was significantly negative with no sex difference and a substantially stronger effect in children older than 5 years. SDS of Cystatin C and hs-TnT showed a significant positive association with a clear difference between the sexes demonstrating a stronger effect in girls. In girls, we did not find an interaction with age, whereas in boys, the effect differed with age. Below 5 years of age, we could not find a significant association. For boys between 5 and 11 years of age, the effect was significantly stronger than for above 11 years.

Germany, consists of a homogenous, predominantly white-Caucasian population. Details about participants, recruitment process and study protocol have been published previously (7, 8, 9). Pubertal stages have been assessed according to Tanner stages through clinical examination by a pediatrician.

The LIFE Child study was designed in conformity with the Declaration of Helsinki and its later amendments (10) and is registered with ClinicalTrial.gov (NCT02550236). The study protocol was approved by the Ethical Committee of the Medical Faculty, University of Leipzig (Reg. No. 264-10-19042010). The Ethical Committee is registered as an Institutional Review Board with the Office for Human Research Protection (IORG0001320 and IRB00001750). Written informed consent was obtained from all parents and children over the age of 12 (8).

In conformity with our study about age-dependent reference values for hs-TnT and NT-proBNP, children with known cardiac disease ($n=23$, 88 blood samples), children who took cardiovascular medications including digoxin, antihypertensives or anticoagulants ($n=10$, 22 blood samples) and 13 outliers (>99.75th age- and sex-adjusted percentile for hs-TnT and NT-proBNP) were excluded from the analysis. We also excluded the levels of IGF-1, IGF-BP3, HbA1c and CysC that were above or below 3.5 standard deviation scores (SDSs) (IGF-1: $n=6$ values from 6 children (1 male); IGF-BP3: $n=10$ values from 10 children (7 males); CysC: $n = 13$ values from 13 children (8 males); HbA1c: $n=20$ values from 19 children (8 males)).

Laboratory values

Blood withdrawal was performed according to study protocol (9). Serum hs-TnT and NT-proBNP concentrations were measured as described previously (7) by the Institute of Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics of the University of Leipzig, in accordance with manufacturer's protocol on an automated laboratory analyzer Cobas 8000 e602 (Roche Diagnostics), with an electrochemiluminescence immunoassay based on sandwich principle (Roche Diagnostics). Primary measuring ranges were 5–35,000 ng/L for NT-proBNP assay and 5–10,000 ng/L for hs-TnT assay until conversion to troponin hs-STAT-test on Cobas 8000 e801 in 2018, where primary measuring range was 3–10,000 ng/L.

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Table 1 Descriptive statistics of our cohort and laboratory values presented as count (percent) for categorical variables and mean (standard deviations) for continuous variables.

	(ALL), ***n*** **= 4947**	**Male, *n* = 2508**	**Female, *n* = 2439**	***P*-value**
Age (years)	9.07 (5.70)	8.75 (5.39)	9.40 (5.99)	<0.001
hs-troponin T (ng/L)	4.40 (8.66)	4.64 (11.5)`	4.16 (4.19)	0.063
hs-troponin T values:				<0.001
Below detection limit	2241 (50.6%)	993 (44.5%)	1248 (56.8%)	
Exact value	2190 (49.4%)	1239 (55.5%)	951 (43.2%)	
NT-proBNP (pg/mL)	83.6 (71.1)	81.6 (72.7)	85.7 (69.4)	0.046
NT-proBNP values:				<0.001
Below detection limit	60 (1.26%)	48 (2.00%)	12 (0.51%)	
Exact value	4684 (98.7%)	2349 (98.0%)	2335 (99.5%)	
IGF-I-SDS	0.03 (1.05)	0.02 (1.04)	0.03 (1.06)	0.584
IGF-BP3-SDS	0.24 (0.95)	0.24 (0.99)	0.24 (0.91)	0.917
HbA1c-SDS	−0.02 (1.04)	−0.02 (1.03)	−0.02 (1.04)	0.963
Cystatin C-SDS	−0.18 (1.02)	−0.18 (1.02)	−0.18 (1.02)	0.932

Comparison measurements between hs-TnT and troponin hs-STAT-test showed very good accordance (Passing–Bablok regression ($y = -0.306260 + 0.976927\ x$), Spearman's coefficient 0.997 > 0.95).

Statistical analysis

Descriptive statistics are presented as count (percent) for categorical variables and mean (standard deviations) for continuous variables. Obtained values below the detection were reported as the lower limit of detection and marked as left-censored (values below the limit of detection: NT-proBNP: n = 58 out of 4648; hs-TnT: n = 215 out of 366; and n = 2002 out of 3971 samples below the new detection limit after assay conversion to Troponin hs-STAT-test in 2018) (Table 1).

In our previous study, we estimated reference ranges for NT-proBNP and hs-TnT. These references were used to transform the measured values into age- and sex-adjusted SDS, where 0 represents the expected value and ±1 indicates a value 1 standard deviation above/below the expected value. SDS corresponding to measures below the limit of detection were marked as left censored. HbA1c, CysC, IGF-I and IGF-BP3 values were also transformed into SDS, using the references published in Hovestadt *et al.* (11), Ziegelasch *et al.* (12) and Hörenz *et al.* (13). Associations were assessed using censored generalized additive regression models for location, shape and scale (https://cran.r-project.org/package=gamlss.cens). A left-censored normal distribution was assumed because SDS are normally distributed by design. All associations between continuous variables were checked for non-linearity. All models were adjusted for multiple measurements per child by adding random effects on the intercept and, if necessary, on the slope. All examined main associations turned out to be linear. Therefore, results are presented as slopes (β), slopes for interaction (ia) terms are indicated by ia as subscript (β_{ia}). We also checked for differences in the associations between sexes and age groups. Breakpoints for age were determined by step-wise iteration across the age range. Because the available sample size varies by laboratory measure, we present the sample sizes for each model (n, n_{male}).

All statistical analyses were done using R, version 4.2. (https://www.r-project.org/) The significance level was set to alpha = 0.05.

Results

NT-proBNP

We found a strong association between lower NT-proBNP-SDS and higher IGF-1-SDS ($\beta = -0.22$, $P < 0.0001$, $\beta_{boys} = -0.24$, $P < 0.0001$, $\beta_{girls} = -0.20$, $P < 0.0001$, $n = 3773$ from 2108 children (1068 boys), $n_{boys} = 1914$). When modeling NT-proBNP–SDS dependent on height-SDS, the univariate analysis showed a highly significant negative association between NT-proBNP–SDS and height-SDS ($\beta = -0.08$, $P < 0.0001$). The general relationship between IGF-1–SDS and height-SDS in our cohort was as expected positive with a strong effect ($\beta = 0.36$, $P < 0.0001$). After including height-SDS and IGF-1–SDS into a multivariate model, height-SDS lost its statistical significance whereas IGF-1–SDS interestingly showed the same effect as before ($\beta_{IGF\text{-}1\text{-}SDS} = -0.22$, $P < 0.0001$; $\beta_{height\text{-}SDS} = 0.01$, $P = 0.374$). The association was generally independent of sex and age but showed a significantly stronger effect in youths post-puberty ($\beta = -0.08$, $P = 0.023$) (Fig. 1A).

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The association between NT-proBNP-SDS and IGF-BP3-SDS showed a similarly strong negative relation ($\beta = -0.20$, $P < 0.0001$, $\beta_{boys} = -0.24$, $P < 0.0001$, $\beta_{girls} = -0.15$, $P < 0.0001$, $n = 3791$ from 2112 children (1066 boys), $n_{boys} = 1917$) but a pronounced difference between the sexes ($\beta = 0.08$, $P = 0.0003$). Furthermore, we found a significant age dependency ($\beta_{ia} = -0.13$, $P = 0.0003$). The association between NT-proBNP-SDS and IGF-BP3-SDS was stronger below the age of 13 years ($\beta = -0.23$, $P < 0.0001$) compared to the effect above 13 years ($\beta = -0.09$, $P = 0.0003$). Considering sex, the association was strongly negative under the age of 13 years in both sexes ($\beta_{boys} = -0.26$, $P < 0.0001$; $\beta_{girls} = -0.19$, $P < 0.0001$). However, for children older than 13 years, the association was still present in boys ($\beta_{boys} = -0.15$, $P < 0.0001$) but not in girls ($\beta_{girls} = -0.06$, $P = 0.10$) (Fig. 1B).

NT-proBNP-SDS and HbA1c-SDS showed an inverse association ($\beta = -0.05$, $P < 0.0001$, $n = 4083$ from 2135 children (1093 boys), $n_{boys} = 2089$). The effect did not differ between sexes ($\beta_{ia} = -0.02$, $P = 0.21$) but by age ($\beta_{ia} = -0.07$, $P = 0.0003$). Above 11 years, the effect was stronger ($\beta = -0.10$, $P < 0.0001$) than below 11 years where the association did not reach statistical significance ($\beta = -0.024$, $P = 0.07$) (Fig. 1D).

We could not demonstrate an overall significant relation between the NT-proBNP-SDS and CysC-SDS ($\beta = -0.01$, $P = 0.18$, $n = 4037$, from 2140 children (1092 boys), $n_{boys} = 2050$). However, investigating different age groups, we found a negative association between 5 and 11 years of age ($\beta = -0.07$, $P < 0.0001$) but not for children below the age of 5 years ($\beta = 0.003$, $P = 0.90$) or above 11 years ($\beta = 0.02$, $P = 0.13$) (Fig. 1C).

hs-troponin T

We found a significant positive association between hs-TnT-SDS and IGF-1-SDS. However, the effect size was small ($\beta = 0.02$, $P = 0.042$, $n = 3613$ from 2061 children (1047 boys), $n_{boys} = 1839$) with no dependence on age and minimal differences between the sexes ($\beta_{ia} = 0.024$, $P = 0.042$) (Fig. 2A). We found a similar but stronger association between IGF-BP3-SDS and hs-TnT-SDS ($\beta = 0.08$, $P < 0.0001$, $n = 3632$ from 2112 children (1066 boys), $n_{boys} = 1917$) (Fig. 2B).

In statistical models including height, we could neither detect a significant relationship between hs-TnT-SDS and height-SDS in univariate analysis ($\beta = 0.02$, $P = 0.104$) nor an association in the multivariate model including IGF-1-SDS and height-SDS (height-SDS: $\beta = 0.02$, $P = 0.281$; IGF-1-SDS: $\beta = 0.02$, $P = 0.121$).

The association between hs-TnT-SDS and HbA1c-SDS was significantly negative ($\beta = -0.1$, $P < 0.0001$, $n = 3938$ from 2105 children (1071 boys), $n_{boys} = 2008$) with no difference between the sexes ($\beta_{ia} = -0.01$, $P = 0.66$). The effect was substantially stronger for children older than 5 years ($\beta = -0.12$, $P < 0.0001$). For children younger than 5 years, the effect diminished to $\beta = -0.02$, $P = 0.31$ (Fig. 2D).

Overall, CysC-SDS and hs-TnT-SDS showed a significant positive association ($\beta = 0.16$, $P < 0.0001$, $n_{values} = 3917$ from 2124 children (1079 boys), $n_{values\ males} = 1933$) with a clear difference between the sexes ($\beta = 0.06$, $P = 0.006$) with a stronger effect in girls ($\beta = 0.19$, $P < 0.0001$) than in boys ($\beta = 0.13$, $P < 0.0001$). In girls, we did not find an interaction with age, whereas in boys, the effect differed with age. Below 5 years of age, we could not find a significant association ($\beta_{<5\ years} = 0.05$, $P_{<5\ years} = 0.20$). For boys between 5 and 11 years of age, the effect was significantly stronger ($\beta_{5-11\ years} = 0.19$, $P_{5-11\ years} < 0.0001$) than for boys above 11 years ($\beta_{11-18\ years} = 0.11$, $P_{11-18\ years} < 0.0001$); however, in boys younger than 5 years, there was no significant association at all ($\beta = 0.05$, $P = 0.20$). In girls, the association did not differ between age groups ($\beta = 0.19$, $P < 0.0001$) (Fig. 2C).

In summary, we demonstrated significant and age- and sex-dependent associations between cardiac marker levels (NT-proBNP and hs-TnT) and metabolic markers as represented by IGF-1, IGF-BP3, CysC and HbA1c levels in healthy children with generally stronger and inverse effect sizes regarding NT-proBNP. These results are summarized in Table 2 with the effects we found previously between both cardiac markers and puberty, BMI and lipid levels with the strongest effect demonstrated between NT-proBNP levels and pubertal stages (7).

Discussion

Associations between cardiac markers and growth hormone status in adults

Several studies in adults and especially in adult patients with acromegaly have reported associations between growth hormone markers and cardiac markers together with cardiovascular morbidity and mortality rates. Andreassen *et al.* found concordant results to ours with IGF-1 levels that were inversely associated with NT-proBNP levels in 642 individuals (age 50–89 years). They reported a 16.9% reduction in NT-proBNP levels per twofold increase in IGF-1 level and that both

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Table 2 Metabolic markers are associated with cardiac marker levels (NT-proBNP and hs-TnT) in healthy children (LIFE Child cohort) with stronger effects on NT-proBNP levels. The strongest effect was demonstrated between NT-proBNP levels and pubertal stages (7).

	NT-proBNP	hs-troponin T
BMI	$\beta_{boys} = -0.12$, $P < 0.0001$ $\beta_{girls} = -0.11$, $P < 0.0001$ $\beta_{ia} = -0.001$, $P = 0.56$	$\beta_{boys} = 0.04$, $P = 0.030$ $\beta_{girls} = -0.010$, $P = 0.63$
Pubertal stages	Pubertal stages 1-2 $\beta_{boys} = -33.4$, $P < 0.0001$ $\beta_{girls} = -33.0$, $P < 0.0001$ Pubertal stages 2–3 $\beta_{boys} = -19.7$, $P = 0.0009$ $\beta_{girls} = -16.2$, $P = 0.0001$ Pubertal stages 3–4 $\beta_{boys} = -12.6$, $P = 0.057$ $\beta_{girls} = -9.7$, $P = 0.042$ Pubertal stages 4-5 $\beta_{boys} = -16.1$, $P = 0.009$ $\beta_{girls} = -6.5$, $P = 0.066$	Pubertal stage 1-2: $\beta_{boys} = -1.0$, $P = 0.0007$ $\beta_{girls} = -1.7$, $P < 0.0001$ Pubertal stage 2-5: $\beta_{boys} = 1.9$, $P = 0.000$ Lower levels in girls than boys with increasing effect sizes: $\beta_{p1} = -0.19$, $P = 0.39$ $\beta_{p2} = -0.83$, $P = 0.03$ $\beta_{p3} = -0.61$, $P = 0.28$ $\beta_{p4} = -0.99$, $P = 0.05$ $\beta_{p5} = -2.94$, $P < 0.0001$
IGF-1	$\beta_{boys} = -0.24$, $P < 0.0001$ $\beta_{girls} = -0.20$, $P < 0.0001$ $\beta_{ia} = 0.05$, $P = 0.024$	$\beta = 0.02$, $P = 0.042$ $\beta_{ia} = 0.024$, $P = 0.042$
IGF-BP3	$\beta_{boys} = -0.24$, $P < 0.0001$ $\beta_{girls} = -0.15$, $P < 0.0001$ $\beta_{ia\ sex} = 0.08$, $P = 0.0003$ $\beta_{<13\ years} = -0.23$, $P < 0.0001$ $\beta_{>13\ years} = -0.09$, $P = 0.0003$ $\beta_{ia\ age} = -0.13$, $P < 0.0001$	$\beta = 0.08$, $P < 0.0001$ $\beta_{ia\ sex} = 0.03$, $P = 0.25$
HbA1c	$\beta = -0.05$, $P < 0.0001$ $\beta_{ia\ sex} = -0.02$, $P = 0.21$ $\beta_{ia\ age} = -0.07$, $P = 0.0003$ $\beta_{<11\ years} = -0.024$, $P = 0.07$ $\beta_{>11\ years} = -0.10$, $P < 0.0001$ $\beta_{ia\ sex} = -0.02$, $P = 0.21$	$\beta = -0.1$, $P < 0.0001$ $\beta_{ia\ sex} = -0.01$, $P = 0.66$ $\beta_{ia\ age} = -0.11$, $P < 0.0001$ $\beta_{>5\ years} = -0.12$, $P < 0.0001$ $\beta_{<5\ years} = -0.02$, $P = 0.31$ $\beta_{ia\ sex} = -0.01$, $P = 0.66$
Cystatin C	$\beta = -0.01$, $P = 0.18$ $\beta_{5\text{-}11\ years} = -0.07$, $P < 0.0001$ $\beta_{<5\ years} = 0.003$, $P = 0.9$ $\beta_{>11\ years} = 0.02$, $P = 0.13$	$\beta = 0.16$, $P < 0.0001$ $\beta_{ia\ sex} = 0.06$, $P = 0.006$ $\beta_{girls} = 0.19$, $P < 0.0001$ $\beta_{boys} = 0.13$, $P < 0.0001$ $\beta_{<5years\ boys} = 0.05$, $P = 0.2$ $\beta_{5\text{-}11years\ boys} = 0.19$, $P < 0.0001$ $\beta_{11\text{-}18years\ boys} = 0.11$, $P < 0.0001$
Cholesterol	$\beta_{boys} = -0.11$, $P < 0.0001$ $\beta_{girls} = -0.06$, $P < 0.0001$ $\beta_{ia} = 0.05$, $P = 0.018$	No meaningful association
LDL cholesterol	$\beta_{boys} = -0.08$, $P < 0.0001$ $\beta_{girls} = -0.03$, $P = 0.014$ $\beta_{ia} = 0.05$, $P = 0.014$	$\beta_{boys} = -0.04$, $P = 0.046$ $\beta_{girls} = 0.007$, $P = 0.73$
Triglycerides	$\beta_{boys} = -0.16$, $P < 0.0001$ $\beta_{girls} = -0.11$, $P < 0.0001$ $\beta_{ia} = 0.05$, $P = 0.01$	$\beta_{boys} = -0.044$, $P = 0.018$ $\beta_{girls} = -0.030$, $P = 0.14$

markers were independently predictive of developing congestive HF in their population. Furthermore, high IGF-1 levels were associated with increased all-cause mortality but not with the incidence of cardiovascular disease (14). The inverse relation between IGF-1 levels and the risk for HF in the elderly was also reported by Vasan *et al.* in their cohort of patients who did not have a previous myocardial infarction (15).

The Study of Health in Pomerania (SHIP) explored the relationship between growth hormone markers and markers of cardiovascular disease. Their results, obtained from the largest reported adult cohort to date ($n = 4308$, 20–79 years old), demonstrated that, in women, higher baseline IGF-I values were associated with an increase in NT-proBNP levels. The group did not find the same effect for IGF-BP3, where no association was found.

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In men, they reported that low and high baseline values of IGF-I or IGF-BP-3 were associated with higher NT-proBNP levels (16). Both results are contrary to our findings and the findings of the aforementioned adult studies. Most likely the differences arose from the different study cohort compositions consisting of elderly adults, adults of all ages vs children. Since it is known that IGF-1 levels are age-dependent and show a rapid drop from puberty through the first two decades of life followed by a slower decline (17), age should always be taken into account when interpreting these values.

Another study by Koegelenberg *et al.* affirmed the inverse link between NT-proBNP and IGF-1. While investigating for differences between black and white middle-aged population (160 black and 195 white women and men), they found NT-proBNP and IGF-1 linked inversely in white people but not in their black counterparts, with the association remaining significant after adjustments for age, sex and BMI ($R^2 = 0.39$; $\beta = -0.22$; $P < 0.001$) (18). Unfortunately, we cannot add additional evidence regarding ethnical differences in childhood due to our predominantly white cohort.

To gain more understanding of the interaction between growth hormone status and cardiac markers and cardiac function in general, studies in patients with specific growth hormone disturbances such as acromegaly on the one side and severe growth hormone deficiency on the other side are helpful. The Belgian registry of acromegaly published results supporting evidence that patients with active acromegaly and higher growth hormone levels had significantly lower levels of NT-proBNP compared to patients with controlled acromegaly (47.0ng/L vs 71.0 ng/L; $P < 0.001$). Interestingly, they did not find an influence of the use of somatostatin analogs on NT-proBNP levels (19). Whereas another group studied cardiac effects such as the change of NT-proBNP levels and end-diastolic volume (EDV) after 3 months of acromegaly treatment and found an increase in EDV and in NT-proBNP levels probably reflecting a modification of cardiac function after commencing growth hormone lowering therapy (20).

Associations between growth hormone status in patients with congenital heart disease

There is a paucity of data regarding the influence of growth hormone status or physiological growth on cardiac function and cardiac marker levels in healthy or unwell children. One group investigated associations between IGF-1 and IGF-BP3 and HF in children with left-to-right shunt congenital heart disease (CHD). They found lower IGF-1 and IGF-BP-3 levels in children with CHD compared to the control group ($P < 0.01$). Furthermore, children with CHD and HF had lower levels than children with only CHD ($P < 0.05$) with the lowest IGF-1 levels in the NYHA-IV subgroup ($P < 0.01$). Children with CHD + HF are expected to have high cardiac markers, therefore the result of an inverse correlation in the CHD + HF group between IGF-1 and IGF-BP-3 levels and cTnI levels ($r = -0.692$, $P < 0.05$; $r = -0.530$, $P < 0.05$) (6) seems to be of particular interest. Peng *et al.* proposed low serum IGF-1 levels as an indicator for HF risk in CHD patients. A suggestion that could be taken into consideration in a possible future multifactorial scoring system. Since IGF-1 levels were also reported to be low in other catabolic states such as during perioperative phase in pediatric CHD patients (21) and in adults with critical illness (22), IGF-1 would probably not be reliable as a single marker.

In our cohort of healthy children, we found positive associations between hs-TnT and IGF-1 and IGF-BP3. This could be due to the cardiac marker levels being within normal range in our cohort and the general difference between sick and healthy children.

The inverse correlation between NT-proBNP and IGF-1 levels shown in our data is supported by the findings demonstrated by Avitabile *et al.* in CHD patients following Fontan procedure ($n = 50$; median age 11.1 years). Lower IGF-1 levels were also associated with longer interval since Fontan and lower systemic flow (23).

Growth hormone therapy in children with congenital heart diseases

The found associations also contribute to the topic of growth hormone (GH) therapy in children with CHD, which is an evolving research field. Several small studies have investigated GH therapy in these patients; this seems to be a promising treatment option to improve patient outcomes, especially in CHD patients with HF and/or failure to thrive.

Nygren *et al.* were able to demonstrate expression of IGF-1 and growth hormone receptor (GH-R) mRNA in the tissue of 18 children undergoing surgery for congenital heart disease. They found a positive correlation between GH-R mRNA and standardized weight, BMI and standardized BMI. For IGF-I mRNA, only an association with BMI was seen. These results suggest a role for GH therapy in these patients (24).

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Isgaard *et al.* reviewed studies discussing the role of GH treatment in patients with cardiovascular diseases like dilative cardiomyopathy and chronic HF and concluded that hormone therapy offers interesting perspectives for new complementary treatment options (25).

In children with structural abnormalities of the heart, GH therapy seems to be safe, although there is still a lack of long-term data (26). A three-year follow-up study in children with Noonan's syndrome ($n=23$) who received GH therapy showed that none of them developed hypertrophic cardiomyopathy (27). In a small study following GH treatment in children with failure to thrive post-cardiac transplant, the therapy was considered to be effective and safe as well (28).

Conclusion

In our dataset, obtained from a large cohort of healthy children, we demonstrate significant interactions between cardiac markers (NT-proBNP and hs-TnT) and markers of metabolism and pubertal development (Table 2). We have previously described inverse associations between lower NT-proBNP levels and advancing puberty, higher BMI and higher levels of serum lipids (7). In this study, we could add similar inverse associations between NT-proBNP and levels of HbA1c, IGF-1 and IGF-BP3.

In addition, we demonstrated that some interactions between cardiac and metabolic markers are sex-dependent, with a stronger effect in boys for the associations with IGF-BP3 and lipid levels, and a stronger effect in girls for declines associated with advancing puberty (7), whereas others (HbA1c and BMI) were independent of sex. The biggest effect on cardiac marker levels was seen by pubertal stages. Future studies should investigate these associations further, exploring, for example, the interactions with sex hormones, including a special focus on age and sex dependency.

Our findings of the associations between cardiac marker levels and markers of growth hormone status in healthy children add to an interesting study topic.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committees (Ethical Committee of the University of Leipzig; Reg. No. 264-10-19042010). The LIFE Child study is registered with ClinicalTrial.gov (NCT02550236). Written informed consent was obtained from all parents and children over the age of 12 (8).

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