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Confounding Masks the Relationship Between Thiamine and Quality of Life in Pediatric Congenital Heart Disease: A Multivariable Analysis

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Abstract

Background:

Children with congenital heart disease (CHD) are at risk of impaired quality of life (QoL) due to hemodynamic burden and nutritional disturbances. Thiamine plays an essential role in myocardial energy metabolism, but its association with QoL in pediatric CHD remains unclear. This study aimed to evaluate the relationship between thiamine levels and QoL in children with CHD with left-to-right shunt lesions.

Methods:

A cross-sectional study was conducted in children aged 2–18 years at a tertiary referral center. Thiamine levels were measured using laboratory assays, and QoL was assessed using the Pediatric Quality of Life Inventory (PedsQL). Associations were analyzed using Spearman's correlation and multivariable linear regression, adjusting for age, sex, and ejection fraction.

Results:

Fifty-six children were included (median age 7.27 years; 64.3% female). The median PedsQL score was 72.9 (IQR 63.7–87.3). A weak, non-significant correlation was observed between thiamine levels and QoL ($\rho = -0.216$, $p = 0.109$), which remained non-significant after adjustment (partial $\rho = -0.215$, $p = 0.122$). In multivariable analysis, thiamine was not independently associated with QoL ($\beta = -0.0039$, $p = 0.502$; $R^2 = 0.04$). A significant correlation in the physical domain ($\rho = -0.319$, $p = 0.017$) was not maintained after adjustment.

Conclusions:

The apparent association between thiamine levels and QoL is likely confounded by clinical factors. Thiamine alone is not an independent predictor of QoL in pediatric CHD, highlighting the importance of multivariable analysis in interpreting nutritional associations.

INTRODUCTION

Congenital heart disease (CHD) is the most common congenital anomaly worldwide and remains a major contributor to morbidity in the pediatric population [1, 2]. Advances in surgical and medical management have markedly improved survival rates, shifting the focus of care beyond mortality toward long-term outcomes such as quality of life (QoL) [3, 4]. As a result, QoL has emerged as a critical endpoint reflecting not only physical health but also emotional, social, and functional well-being in children with CHD [5–7].

Children with CHD, particularly those with left-to-right shunt lesions, are exposed to chronic hemodynamic stress that may lead to heart failure, impaired exercise tolerance, and increased metabolic demands. These physiological disturbances are frequently accompanied by nutritional challenges, including both macronutrient deficiencies and micronutrient imbalances [8, 9]. Malnutrition has been consistently associated with poorer functional capacity and reduced QoL in this population, highlighting the importance of nutritional status as a modifiable factor in long-term outcomes [10].

Thiamine (vitamin B1) is an essential water-soluble micronutrient that plays a central role in cellular energy metabolism, particularly in myocardial tissue with high energy demands [11, 12]. As a cofactor in key enzymatic pathways such as pyruvate dehydrogenase and the citric acid cycle, thiamine is crucial for efficient adenosine triphosphate production. Deficiency of thiamine has been linked to impaired myocardial function, increased lactate production, and reduced exercise capacity [13]. In children with CHD, the risk of thiamine deficiency may be further exacerbated by increased metabolic requirements, inadequate nutritional intake, and chronic use of diuretics that enhance urinary excretion of water-soluble vitamins [14, 15].

Despite the biological plausibility linking thiamine status to cardiac function and functional capacity, evidence regarding its relationship with QoL remains limited and inconsistent. Studies in adult heart failure populations have shown mixed results, with some reporting improvements in cardiac function but not necessarily in QoL outcomes following thiamine supplementation [16–18]. In pediatric CHD populations, data are even more scarce, and the extent to which thiamine contributes to QoL independently of other clinical factors is not well understood [6, 19].

Furthermore, previous studies have often relied on unadjusted analyses, which may overestimate associations due to confounding variables such as age, disease severity, and cardiac function. Given the multifactorial nature of quality of life, it remains unclear whether observed associations between thiamine levels and QoL reflect true biological effects or are primarily driven by underlying clinical factors. Therefore, this study aimed to evaluate the association between thiamine levels and QoL in children with congenital heart disease with left-to-right shunt lesions, and to determine whether this relationship persists after adjustment for relevant confounders [20, 21].

Given the multifactorial nature of QoL and the potential for confounding in observational studies, it remains unclear whether previously observed associations reflect true biological effects or are driven by underlying clinical factors. Therefore, this study aimed not only to evaluate the association between thiamine levels and QoL in children with CHD with left-to-right shunt lesions, but also to determine whether unadjusted relationships may be misleading in this context.

Methods

Study Design and Setting

This study employed an analytical observational design with a cross-sectional approach. The study was

conducted at a tertiary referral hospital, including the pediatric outpatient clinic, inpatient wards, and integrated cardiac center. Laboratory analyses were performed at the hospital's central laboratory.

Study Population

Children aged 2–18 years diagnosed with congenital heart disease (CHD) with left-to-right shunt lesions were consecutively recruited between January and December 2025. Eligible diagnoses included atrial septal defect (ASD), ventricular septal defect (VSD), and patent ductus arteriosus (PDA), confirmed by echocardiography.

Inclusion and Exclusion Criteria

Inclusion criteria were: (1) children aged 2–18 years; and (2) confirmed diagnosis of CHD with left-to-right shunt accompanied by heart failure based on Ross or NYHA classification.

Exclusion criteria included: (1) presence of other congenital or structural heart diseases requiring immediate surgical intervention; and (2) presence of genetic syndromes, hereditary disorders, or other chronic systemic diseases.

Sample Size and Sampling Technique

The minimum sample size was calculated based on correlation analysis assumptions, yielding a required sample of 47 subjects. After accounting for a 15% potential dropout, the final minimum sample size was 54 participants. A non-probability consecutive sampling method was applied, whereby all eligible subjects presenting during the study period were included until the required sample size was achieved.

Data Collection

Demographic and clinical data collected included age, sex, diagnosis, and ejection fraction (EF) measured by echocardiography. Thiamine levels were measured using standardized laboratory assays from blood samples. Quality of life (QoL) was assessed using the validated Pediatric Quality of Life Inventory (PedsQL), which evaluates physical, emotional, social, and school functioning domains. Both child self-reports and parent proxy-reports were obtained when applicable. Defect size was categorized based on echocardiographic measurement as small (<5 mm), moderate (5–10 mm), and large (>10 mm) for descriptive analysis.

Variables

The independent variable was serum thiamine level. The dependent variable was total QoL score measured using PedsQL. Covariates included age, sex, and ejection fraction as indicators of clinical status.

Statistical Analysis

Data were analyzed using statistical software. Continuous variables were summarized as median and interquartile range (IQR) due to non-normal data distribution, as assessed using the Shapiro–Wilk test. Categorical variables were presented as frequencies and percentages.

The association between thiamine levels and quality of life (QoL) was evaluated using Spearman's rank correlation. To account for potential confounding, partial Spearman correlation analysis was performed adjusting for age, sex, and ejection fraction (EF). Multivariable linear regression analysis was conducted to assess the independent association between thiamine levels and QoL, with results reported as regression coefficients (β) and corresponding p-values.

Group comparisons were performed using the Kruskal–Wallis test for multiple groups and the Wilcoxon rank-sum test for two-group comparisons. Multicollinearity was assessed using the Variance Inflation Factor (VIF), with values close to 1 indicating no significant multicollinearity. Exploratory analyses were conducted to evaluate factors associated with thiamine levels, and the results are presented in the Supplementary Material. A p-value < 0.05 was considered statistically significant (Supplementary Material Table S2)

Ethical Considerations

This study was approved by the Institutional Ethics Committee. Written informed consent was obtained from parents or legal guardians prior to participation. All procedures were conducted in accordance with ethical standards and the Declaration of Helsinki.

Results

Baseline Characteristics

A total of 56 children with congenital heart disease (CHD) with left-to-right shunt lesions were included in the analysis. The median age was 9 years (range 1–18 years), and the majority were female (64.3%). The most common diagnosis was ventricular septal defect (VSD) (50.0%), followed by patent ductus arteriosus (PDA) (30.3%) and atrial septal defect (ASD) (19.6%).

The median thiamine level was 300.01, and the median ejection fraction was 66.6% (IQR 60.7–72.1). The median total Pediatric Quality of Life Inventory (PedsQL) score was 72.9 (IQR 63.7–87.3). The baseline demographic and clinical characteristics of the study population are presented in Table 1. Detailed distributions of QoL scores by domain and respondent type are provided in Supplementary Table S1.

Table 1
Baseline Demographic and Clinical Characteristics of the Study Population

Characteristic	Value
Sex, n (%)	
Male	19 (33.9)
Female	37 (66.1)
Age (years)	9 (1–18)
Body Weight (kg)	18 (7.8–68)
Height (cm)	124 (73–170)
Diagnosis, n (%)	
ASD	11 (19.6)
VSD	28 (50.0)
PDA	17 (30.4)
Defect Size, n (%)	
Small (< 5 mm)	35 (62.5)
Moderate (5–10 mm)	18 (32.1)
Large (> 10 mm)	3 (5.3)
Ejection Fraction (%)	67.5 (52.2–83.4)
Fractional Shortening (%)	36 (25.5–51.3)
Thiamine Level (ng/mL)	300.0 (42.23–1642.23)

Continuous variables are presented as median (range), and categorical variables as frequencies and percentages. Categorical variables are presented as frequencies and percentages. Thiamine levels are expressed in [unit]. Quality of life (QoL) was assessed using the Pediatric Quality of Life Inventory (PedsQL), with higher scores indicating better quality of life. Ejection fraction (EF) was measured using echocardiography.

Bivariate Analysis

No statistically significant correlation was observed between thiamine levels and total quality of life (QoL) (Spearman's $\rho = -0.216$, $p = 0.109$). The relationship between thiamine levels and total QoL is illustrated in Fig. 1. Among QoL domains, a statistically significant negative correlation was observed between thiamine levels and the physical functioning domain ($\rho = -0.319$, $p = 0.017$). No significant correlations were found in the emotional ($\rho = -0.220$, $p = 0.104$), social ($\rho = -0.231$, $p = 0.086$), or school

domains (ρ = −0.066, p = 0.628). The correlations between thiamine levels and total as well as domain-specific QoL scores are presented in Table 2. Associations between thiamine levels and clinical variables, including a significant correlation with ejection fraction, are presented in Supplementary Table S3.

Table 2
Correlation Between Thiamine Levels and Quality of Life Scores

Variable	Test	Spearman's ρ	P-Value
Total QoL	Spearman	-0.216	0.109
Physical	Spearman	-0.319	0.017
Emotional	Spearman	-0.220	0.104
Social	Spearman	-0.231	0.086
School	Spearman	-0.066	0.628

Correlation analysis was performed using Spearman's rank correlation coefficient (ρ). Correlation coefficients (ρ) and corresponding p-values are presented. Quality of life (QoL) was assessed using the Pediatric Quality of Life Inventory (PedsQL), including total score and domain-specific scores (physical, emotional, social, and school functioning). A p-value < 0.05 was considered statistically significant.

Scatter plot illustrating the relationship between thiamine levels and total quality of life (QoL) scores measured using the Pediatric Quality of Life Inventory (PedsQL) in children with congenital heart disease. Each point represents an individual participant. The solid line represents the fitted trend. No significant correlation was observed (Spearman's ρ = −0.216, p = 0.109), indicating no clear association between thiamine levels and QoL.

No significant differences in total QoL scores were observed across diagnostic groups (Kruskal–Wallis $\chi^2 = 1.52$, p = 0.467), between sexes (Wilcoxon W = 436.5, p = 0.193), or between children with and without thiamine deficiency (Wilcoxon W = 257.5, p = 0.081). Comparisons of QoL scores across clinical variables are summarized in Supplementary Table S4.

Adjusted Analysis

After adjusting for age, sex, and ejection fraction using partial Spearman correlation, the association between thiamine levels and total QoL was attenuated and no longer statistically significant (ρ = −0.215, p = 0.122). The results of the partial correlation analysis are presented in Supplementary Table S5.

Multivariable Regression Analysis

In multivariable linear regression analysis, thiamine levels were not independently associated with total QoL (β = −0.0039, p = 0.502). None of the covariates, including age (p = 0.877), sex (p = 0.218), and ejection fraction (p = 0.648), showed significant associations with QoL. The overall regression model

was not statistically significant (F-statistic p = 0.704) and explained only a small proportion of the variance in QoL (R^2 = 0.04). The low R^2 observed in this model likely reflects the inherently multifactorial nature of quality of life, which is not expected to be explained by isolated biochemical markers. The results are summarized in Table 3, while exploratory analyses of factors associated with thiamine levels are presented in Supplementary Table S2. No significant interaction was observed between thiamine levels and ejection fraction, indicating that the association between thiamine and QoL did not differ across levels of cardiac function.

Table 3
Multivariable Linear Regression Analysis of Factors Associated with Quality of Life

Variable	β	Std Error	p-value
Age (Years)	0.055	1.062	0.616
Sex (Male Vs Female)	2.745	10.806	0.8
Ejection Fraction (EF)	0.356	0.706	0.616
Thiamine	-0.0039	1.732	0.502

Multivariable linear regression analysis was performed to evaluate factors independently associated with quality of life (QoL). Regression coefficients (β), 95% confidence intervals (CI), and p-values are presented. Variables included in the model were thiamine levels, age, sex, and ejection fraction. A p-value < 0.05 was considered statistically significant.

QoL: quality of life; β: regression coefficient.

Sensitivity analyses stratified by ejection fraction yielded consistent findings, with no significant association observed between thiamine levels and QoL (ρ = 0.120, p = 0.379 in the normal EF subgroup), supporting the robustness of the primary results.

Sensitivity analysis excluding extreme thiamine values yielded similar results, with no significant association observed (ρ = −0.257, p = 0.658), indicating that the findings were not driven by outliers.

Multicollinearity Assessment

Variance Inflation Factor (VIF) values for all variables were close to 1, indicating no evidence of multicollinearity among predictors. Exploratory analyses assessing the association between ejection fraction and demographic and clinical variables are presented in Table S6. Exploratory multivariable analyses evaluating factors associated with ejection fraction are presented in Table S7.

Summary of Key Findings

An initial weak correlation between thiamine levels and QoL was observed; however, this association was not sustained after adjustment for clinical variables and was not confirmed in multivariable

analysis. Overall, thiamine levels were not an independent predictor of QoL in this cross-sectional study.

Discussion

The key finding of this study is that the initially observed association between thiamine levels and QoL disappeared after adjustment, suggesting that the observed crude association may be influenced by underlying clinical factors rather than representing an independent effect. This highlights the critical role of confounding in observational studies and suggests that unadjusted associations in pediatric CHD research may overestimate or falsely suggest clinically meaningful relationships [20, 21]. Furthermore, thiamine levels were not identified as an independent predictor of QoL in multivariable analysis. The observed correlation coefficients were small in magnitude, suggesting limited clinical relevance. These findings indicate that the apparent relationship appears to be influenced by underlying clinical factors rather than representing a direct causal association. The absence of a consistent association across subgroup analyses further supports the lack of a robust relationship between thiamine levels and QoL, suggesting that the observed crude associations may be driven by underlying variability rather than a true biological effect. The consistency of results after exclusion of outliers further supports the robustness of the findings and suggests that extreme values did not materially influence the observed associations.

The initial observation of a weak negative correlation between thiamine levels and QoL, particularly within the physical functioning domain, may reflect underlying disease severity rather than a true detrimental effect of thiamine. However, this association did not persist after adjustment for age, sex, and ejection fraction, suggesting that the initially observed relationship was likely driven by confounding clinical factors rather than a direct effect of thiamine. Children with more severe hemodynamic burden or heart failure may have higher metabolic demands, altered nutritional status, or receive more intensive medical therapy, all of which could influence both thiamine levels and physical functioning [8–10]. In line with this, thiamine levels were significantly associated with ejection fraction in our study, suggesting a potential link between thiamine status and cardiac functional parameters. These findings emphasize that reliance on unadjusted analyses may lead to misleading conclusions, particularly in complex clinical conditions such as CHD, where multiple interrelated factors influence outcomes [5, 6].

Our findings are consistent with previous studies in adult heart failure populations, which have reported inconsistent or minimal effects of thiamine supplementation on patient-centered outcomes such as QoL, despite some improvements in surrogate cardiac parameters [16–18]. These discrepancies underscore the complexity of translating metabolic or biochemical changes into meaningful clinical outcomes. In pediatric CHD populations, where QoL is influenced by a broad range of physiological, developmental, and psychosocial factors, the contribution of a single micronutrient is likely to be limited [6, 7, 9].

Thiamine plays a well-established role in myocardial energy metabolism and cellular function. Deficiency has been associated with impaired oxidative metabolism, increased lactate production, and reduced cardiac efficiency [11–13]. However, the absence of an independent association in this study suggests

that, within the observed range of thiamine levels, variations in thiamine status may not be sufficient to significantly impact overall QoL. Alternatively, it is possible that thiamine influences intermediate physiological parameters, such as cardiac function or exercise tolerance, without translating into measurable differences in patient-reported outcomes.

Importantly, the attenuation of the association after adjustment highlights the critical role of confounding in observational studies. Factors such as age, cardiac function, and disease severity are known to strongly influence QoL in children with CHD and may overshadow the potential contribution of nutritional variables [5–7]. This finding emphasizes the need for cautious interpretation of unadjusted correlations, which may overestimate clinically meaningful relationships. Future studies should prioritize robust analytical approaches, including multivariable modeling and longitudinal designs, to better delineate causal pathways [20].

The clinical implications of this study are noteworthy. Our findings suggest that QoL in children with CHD cannot be adequately explained by a single biomarker such as thiamine. While optimizing nutritional status remains an essential component of comprehensive CHD management, thiamine levels alone may not serve as a reliable biomarker or therapeutic target for improving QoL [9, 12]. Instead, QoL appears to be determined by a complex interplay of clinical, functional, and psychosocial factors, highlighting the need for a multidimensional approach in both assessment and management [6, 10].

This study has several limitations. First, the cross-sectional design precludes causal inference and limits the ability to assess temporal relationships between thiamine status and QoL. Second, the sample size was relatively modest, which may reduce statistical power to detect small but clinically relevant effects. Third, potential residual confounding cannot be entirely excluded, as variables such as disease severity, nutritional intake, and medication use were not comprehensively quantified. Finally, QoL assessment using PedsQL, while validated, may not capture all dimensions relevant to children with CHD [6].

Despite these limitations, this study provides important insights into the relationship between micronutrient status and patient-centered outcomes in pediatric CHD. To our knowledge, this is among the first studies to demonstrate that an initially observed association between a micronutrient and QoL may disappear after appropriate adjustment, highlighting a confounding-driven relationship. This finding underscores the importance of distinguishing between crude and adjusted analyses when interpreting observational data in pediatric cardiology research [20, 21].

Future research should consider longitudinal designs to evaluate changes in thiamine status over time and their relationship with clinical progression and QoL trajectories. Interventional studies assessing targeted nutritional supplementation in selected high-risk subgroups may also help clarify whether specific populations could benefit from such strategies [16, 17]. Additionally, integrating objective functional measures, such as exercise capacity, with patient-reported outcomes may provide a more comprehensive assessment of clinical impact.

In conclusion, while an apparent association between thiamine levels and QoL was observed, this relationship was not independent after adjustment for clinical factors. These findings suggest that thiamine is not a primary determinant of QoL in children with CHD and highlight the importance of considering confounding and multidimensional influences when evaluating nutritional biomarkers in clinical research. In addition, no interaction was observed between thiamine levels and ejection fraction, indicating that the relationship between thiamine and QoL was consistent across different levels of cardiac function.

Conclusion

This study demonstrates that an apparent association between thiamine levels and QoL is not independent and is likely driven by confounding. These findings suggest that unadjusted associations between micronutrient levels and QoL in pediatric CHD may be misleading and underscore the importance of rigorous analytical approaches to distinguish true effects from confounded relationships. Overall, QoL in children with congenital heart disease appears to be influenced by multidimensional factors beyond micronutrient status alone. Future research should focus on longitudinal and interventional approaches to better define the role of nutritional factors within the broader clinical context.

Abbreviations

Abbreviations used in this study include CHD (congenital heart disease), QoL (quality of life), PedsQL (Pediatric Quality of Life Inventory), EF (ejection fraction), ASD (atrial septal defect), VSD (ventricular septal defect), PDA (patent ductus arteriosus), IQR (interquartile range), and CI (confidence interval).

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Universitas Sumatera Utara (Approval No. 375/KEPK/USU/2025). Written informed consent was obtained from parents or legal guardians prior to participation.

Consent for publication
Not applicable.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JK contributed to study conception and design, data extraction, statistical analysis, and manuscript drafting. PA, TCT, RA, and HZA contributed to literature search, data curation, figure generation, risk of bias assessment, and manuscript revision. All authors read and approved the final manuscript.

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Figures

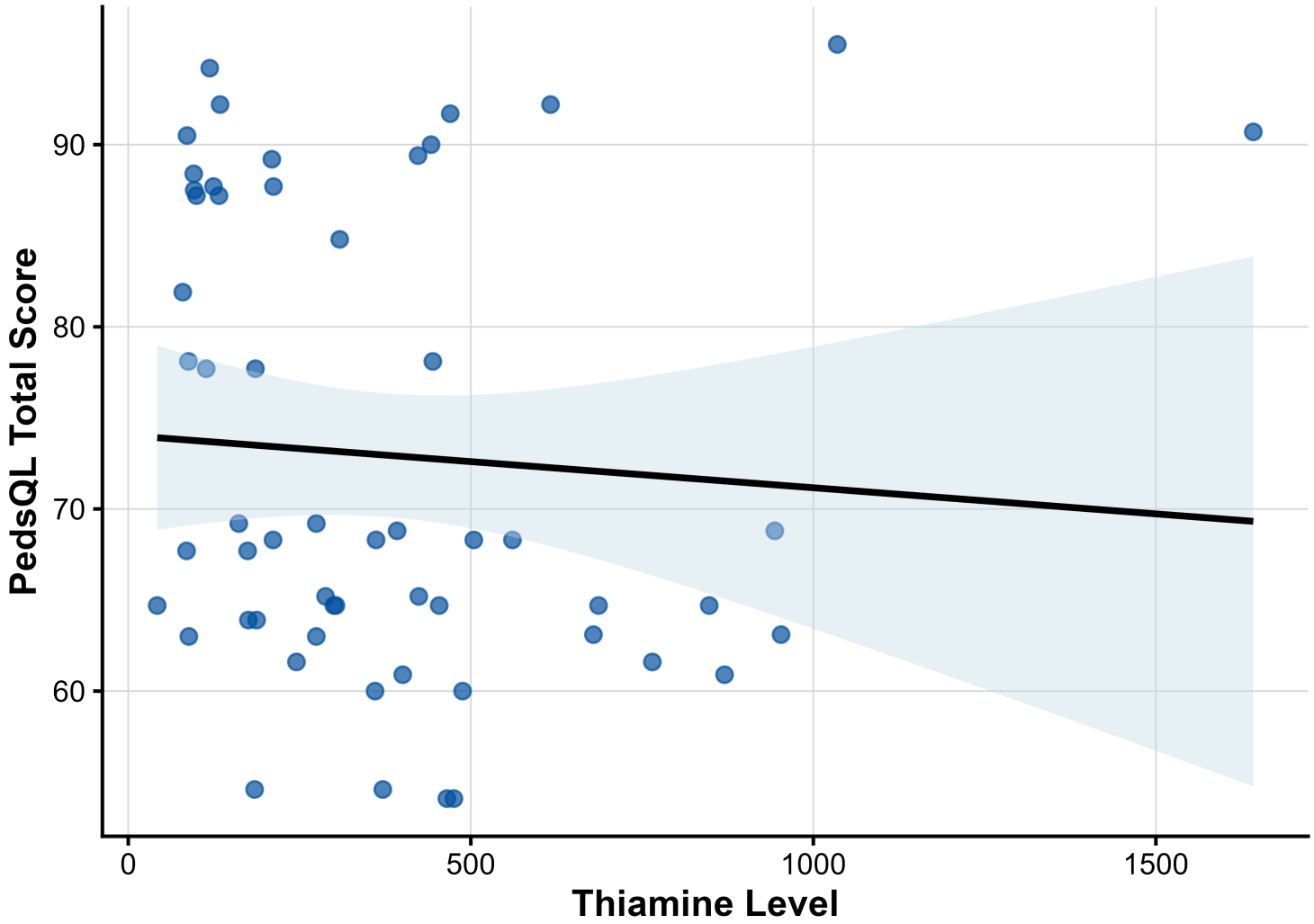


Figure 1

Association Between Thiamine Levels and Total Quality of Life Scores in Children with Congenital Heart Disease

Supplementary Files

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