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Iron Deficiency as Risk Factor for Adverse Cardiovascular Outcomes in Pediatric Heart Disease: A Systematic Review and Meta-Analysis

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Abstract

Background: *Iron deficiency (ID) is associated with increased mortality, reduced exercise capacity, and poorer quality of life in adults with heart failure. Although ID is the most common micronutrient deficiency in children, its association with clinical outcomes in individuals under 21 years of age with heart disease remains poorly defined.To evaluate the association between iron deficiency and adverse cardiovascular outcomes (ACV)—defined as death, mechanical circulatory support, or heart transplant—and to estimate the prevalence of ID in individuals under 21 years of age with heart disease.*

Methods: *A comprehensive search of PubMed, EMBASE, and Web of Science was conducted until December 2024. Studies including participants under 21 with heart disease assessing ID and ACV were included. Studies were excluded if they reported data from adults or animals, if only abstract data were available, or if they were published in a non-English language. Prevalence was summarized using a weighted mean and 95% confidence interval (CI). The pooled association between ID and ACV was estimated using odds ratios (ORs) with 95% CIs under a random-effects model. Heterogeneity was assessed using Cochran's Q and I^2 statistics, and publication bias was explored using funnel plots. Risk of bias was assessed using the ROBINS-E tool.*

Results: *Five retrospective, single-center studies (N=344) were included. ID prevalence ranged from 46.1% to 96.4%, with a weighted mean prevalence of 58.7% (95% CI 53.7–63.7). Three studies reporting ACV outcomes demonstrated that ID was significantly associated with ACV, with a pooled OR of 4.44 (95% CI 2.03–9.71; P<0.001) and low statistical heterogeneity (I^2=16.25%). However, the ability to detect heterogeneity was limited by the small number of studies. All included studies demonstrated a high risk of bias, primarily related to selection bias, missing data, and residual confounding.*

Conclusion: *Iron deficiency is highly prevalent among individuals under 21 years of age with heart disease and is associated with an approximately fourfold increase in the risk of adverse cardiovascular outcomes. The substantial risk of bias across studies limits the generalizability of these findings, underscoring the need for well-designed prospective studies to clarify the role of ID in pediatric heart disease.*

Introduction

Pediatric heart disease is defined as any structural, functional, or congenital cardiac abnormality leading to compromised myocardial function or circulation, encompassing conditions such as congenital heart disease (CHD) and acquired cardiomyopathies. In the pediatric population, CHD and cardiomyopathy are the common causes of heart failure (HF). (Jayaprasad, 2016) Pediatric HF is a complex clinical condition characterized by insufficient cardiac performance in relation to the patient's circulatory requirements. (Rossano et al., 2012) This leads to symptoms and complications that increase the risk of hospitalization, healthcare costs, and elevated rates of morbidity and mortality, underscoring the severe impact on both the healthcare system and the quality of life for affected children and their families. (Amdani et al., 2022)

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In children hospitalized with HF, several factors increase the risk of mortality. These include neonatal presentation, having CHD, and requiring advanced therapies like intravenous vasoactive support, invasive ventilation, or mechanical circulatory support (MCS). (Lasa et al., 2020; Parikh et al., 2019; Ponikowski et al., 2016; Shamszad et al., 2013) In children with dilated cardiomyopathy (DCM), high natriuretic peptide levels, severe growth restriction, and left ventricular systolic dysfunction are linked to adverse cardiovascular outcomes (ACV), defined as death, need for MCS, or heart transplant (HT). (Auerbach et al., 2010; Medar et al., 2015; Price et al., 2006; Towbin et al., 2006; Wong et al., 2011) Emerging evidence from previous pediatric studies suggests that iron deficiency (ID) may also be associated with ACV in individuals younger than 21 with heart disease. (Higgins et al., 2017; Puri et al., 2020) Although CHD and cardiomyopathies differ in etiology and progression, their shared clinical trajectory toward HF and end-stage complications, such as the need for MCS or HT, provides a common framework for evaluating the role of ID. This approach is consistent with other studies in the field that analyze both etiologies together due to their shared pathophysiological pathways leading to HF. (Lasa et al., 2020)

ID is the most common micronutrient deficiency in children worldwide, and it is associated with multiple adverse effects, including neurodevelopmental disorders, immunologic deficiencies, failure to thrive, and anemia. (Archived, n.d.; Mantadakis, 2016) Regarding the influence of iron metabolism on HF, it is well established that a proper iron distribution is fundamental for heart function since iron overload and deficiency contribute to myocardial damage and HF. (Kozłowska et al., 2022; Moscheo et al., 2022) In adults with HF, ID is considered a risk factor for adverse events, regardless of hemoglobin levels.

The estimated prevalence of ID is over 50% in ambulatory patients with chronic HF. (von Haehling et al., 2019; Wong et al., 2016) International guidelines recommend the assessment of ID and repletion if necessary for adults with chronic HF, regardless of anemia. (Heidenreich et al., 2022) Although robust evidence exists in adult populations with HF, where iron deficiency is a well-established risk factor for adverse outcomes, it remains unclear whether these findings can be extrapolated to pediatric patients. Children and adolescents with heart disease differ from adults in terms of cardiac physiology, iron metabolism, growth and developmental stages, and responses to treatment. For pediatric patients, no previous systematic review has examined the association between ID and ACV outcomes, and international guidelines only consider treating ID if it is linked with anemia. (Kirk et al., 2014) This underscores the need for pediatric-specific evidence to guide clinical decision-making.

Given the high prevalence of ID, a potential risk factor for ACV in pediatric heart disease, and limited evidence supporting the strength of association between these, this systematic review aims to synthesize existing literature to explore the relationship between ID and ACV outcomes and assess the prevalence of ID in individuals under 21 with heart disease. We hypothesized that individuals under 21 with concomitant heart disease and ID will have a higher risk of developing ACV outcomes compared to those not exposed. Additionally, we expect the prevalence of ID in this study's sample to exceed 38.6%, a threshold based on a previous U.S. study that reported this prevalence in a representative sample of female participants aged 12–21 years. (Weyand et al., 2023)

Materials and Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P) and was reported according to the PRISMA 2020 statement. (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 Statement - PMC, n.d.; PRISMA 2020 (Checklist, n.d.) The PRISMA 2020 checklist is in Supplementary Information 1. The protocol was registered with PROSPERO (CRD42024543116).

Inclusion Criteria

The inclusion criteria were based on the PECOS framework, including Population, Exposure, Comparison, Outcome, and Study Design as presented in Table 1.

This review defines "children" and "pediatric patients" as individuals under 21 years of age. This threshold aligns with the United States Food and Drug Administration's definition for medical device development, although other organizations like the NIH and UNICEF define "children" as under 18. (Convention on the Rights of the Child Text | UNICEF, n.d.; EU Action on the Rights of the Child - European Commission, n.d.; Health, 2024) The broader age range helps include relevant studies that consider patients up to 21 years old.

ID was defined using multiple iron study criteria, as recommended by previous pediatric HF studies and the National Health and Nutrition Examination Survey. This approach is more appropriate for the pediatric population than the single ferritin-based criteria used in adults because acute and chronic inflammatory conditions in children can affect ferritin

Population	Individuals under 21 years diagnosed with heart disease, including current or previous diagnoses of any structural, functional, or congenital cardiac anomaly, or a history of HT
Exposure	ID is defined as the presence of ≥2 of the following four criteria: serum iron <50 µg/dL, serum ferritin <20 ng/mL, transferrin >300 ng/mL, and transferrin saturation (TSAT) <15%. (Higgins et al., 2017; Puri et al., 2020)
Comparison	No ID
Outcome	ACV (death, HT, or implementation of MCS or ventricular assist device (VAD))
Study Design	Observational (cohort, case-control, cross-sectional) and randomized controlled studies.

Table 1: *Inclusion criteria.*

and transferrin levels. (Looker et al., 1995) Therefore, to reduce misclassification due to inflammation, a combination of biomarkers was used. Specifically, ID was defined as the presence of two or more of the following: serum iron <50 μg/dL, ferritin <20 ng/mL, transferrin >300 ng/mL, and transferrin saturation (TSAT) <15%. This multi-marker definition aligns with pediatric clinical research and large-scale population surveys like the National Health and Nutrition Examination Survey. (Looker et al., 1995; Puri et al., 2020) If multiple iron studies were not available, the definition of ID was recorded, and the study was included if it fulfilled the other criteria.

The use of ACV outcomes as the main outcome was based on its relevance in pediatrics, as previous pediatric studies—not only those related to ID—have used the same outcome in their analyses. (Lasa et al., 2020; Medar et al., 2015; Phillips et al., 2023; Price et al., 2006; Puri et al., 2020)

Exclusion Criteria

Studies including data from adults and animals, and those published in a non-English language or available only as abstracts, were excluded from this analysis. Likewise, study protocols and grey literature were not included in this review.

Information Sources and Search Terms

Titles and abstracts were searched in PubMed, Excerpta Medica Database, and Web of Science to systematically identify relevant studies. The search terms were based on those used in previous papers on HF, CHD, DCM, ACV outcomes, and ID in pediatric populations, with adult HF meta-analyses providing additional terms. The search covered the databases from their inception until December 10th, 2024. The full search strategy is provided in Supplementary Information 2.

Selection Process

All articles from each database search were uploaded to Rayyan® to remove duplicates. (Ouzzani et al., 2016) Titles and abstracts were systematically assessed against inclusion and exclusion criteria, documenting all reasons for exclusion. Relevant articles underwent full-text review. Studies meeting all criteria, but lacking ACV rate data, were included to evaluate the secondary aim of determining the prevalence of ID in the study population. Finally, a CONSORT diagram was created to detail the study selection process and the number of articles included in the review.

Study Risk of Bias Assessment

The ROBINS-E tool was used to assess the quality and risk of bias in the included articles, evaluating domains such as confounder bias, measurement bias for both exposure and outcome, selection bias, post-exposure intervention bias, and reporting bias. (Higgins et al., 2024) The overall risk of bias, including the potential direction and magnitude of bias that could impact results and validity, was also assessed. All assessments were conducted by two assessors (K.L.L. and E.V.S.); a third reviewer (P.K.) resolved any conflicting assessments.

Data Extraction

The information on each study was systematically extracted (K.L.L.), and included: 1) Study characteristics: first authors' last name, year, location, inclusion criteria, exclusion criteria, and study design. 2) Participant demographics: sample size, age, type of heart disease, and follow-up time. 3) Exposure: Definition of ID and its prevalence. 4) Outcome: frequency and proportion of ACV. 5) Secondary outcomes: cumulative length of stay at 3 and 6 months of follow-up from the time of iron testing. 6) Main findings.

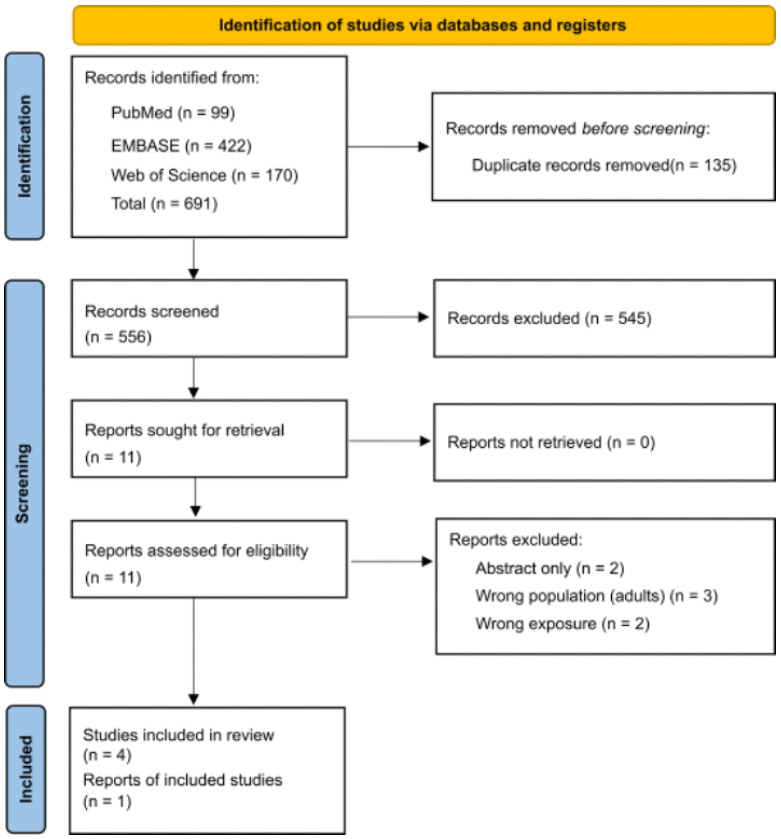

Figure 1: *PRISMA diagram of study selection.*

Narrative Review

The main characteristics of the population, including sample size, main type of heart disease, prevalence of ID, and ACV outcome, were summarized in this analysis. Results were described in subheadings, including ACV outcomes and ID prevalence.

Data Synthesis: Meta-Analysis

For the ACV outcome, odds ratios (OR) with 95% confidence intervals (CI) were estimated by performing a logistic regression model for each study using raw frequencies, with ID as the exposure and ACV as the categorical outcome. Heterogeneity was assessed using Cochran's Q and I^2 statistics. For Cochran's Q, a p-value of <0.1 was considered significant, and for I^2, a value >50% was used as the threshold to indicate substantial heterogeneity, as recommended by Cochrane. (Chapter 10, n.d.) Considering the heterogeneity within the pediatric population with heart disease, a random-effects model meta-analysis was used to pool the data, with between-study variance estimated using the Restricted Maximum Likelihood (REML) method. REML was chosen because it provides less biased estimates of heterogeneity compared with alternative approaches, particularly when the number of studies is small. (Piepho et al., 2024) Publication bias was evaluated with a funnel plot. The prevalence of ID was summarized using a weighted mean and 95% CI. A one-sample proportion test assessed whether the prevalence was significantly higher than 38.4% in this sample. For studies reporting multiple ID prevalences due to different definitions, weighted means and one-sample proportion tests were conducted for each scenario. All analyses, except for heterogeneity assessment (P<0.1), maintained a significance level of 0.05 (alpha) and were performed using STATA 18 software.

Subgroup analysis was planned to evaluate the robustness of the main results, including stratification by sex (female vs. male), type of heart disease (CHD vs. cardiomyopathy), presence of missing exposure data (presence vs. absence), study quality (high vs. low), level of bias (high vs. low), and study design (randomized vs. observational).

Results

Study Selection

The literature search yielded 691 records. After deduplication, 556 records were screened by title and abstract. Following this screening, 11 records were included for full-text screening, of which four studies met the inclusion criteria for this review.

Author and Date	Setting	Aim	ID Definition	Outcome	Study Design	Sample Size	Main Findings
Higgins, 2017 (Higgins et al., 2017)	Seattle, Washington, USA	Examine the ID prevalence and clinical outcomes associated with ID in children with DCM.	Ferritin <100 ng/mL alone or ferritin 100 to 300 ng/mL and TSAT <20%.	Composite outcome is defined as either mortality or need for MCS.	single-center, retrospective observational cohort	28	Log transformed ferritin level was associated with mortality (0.29 (95%CI 0.12,0.70), P=0.006) and composite outcome (0.53 (95% CI 0.35,0.81), P=0.003).
Puri, 2020. (Puri et al., 2020)	Houston, Texas, USA	Determine whether ID is associated with ACV outcome.	Presence of two of the four criteria: serum iron <50 mg/dL, serum ferritin <20 ng/mL, transferrin >300 ng/mL, and TSAT <15%.	ACV defined as the need for VAD implantation, HT, or death.	single-center, retrospective observational cohort	107	ID was associated ACV outcome at six-months follow-up in patients with biventricular physiology (76% ID ACV vs 35% ID in non-ACV, P = 0.002, OR 7, 95% CI 2-24) and single ventricular physiology (79% ID in ACV vs 29% ID in non-ACV, P = 0.014, OR 8, 95% CI 2-32).
Phillips, 2023. (Phillips et al., 2023)	New York, New York, USA	Evaluate the prevalence and harmful effects of ID in children with HF and DCM.	TSAT <20%	ACV is defined as the need for VAD implantation, HT, or death.	single-center, retrospective observational cohort	47	ID was not associated with ACV outcome in the 6 months following laboratory iron testing (HR 1.365, 95% CI 0.612-3.043, P = .447).
Luxford, 2024 (Luxford et al., 2024)	Sydney, Australia	Evaluate the prevalence of ID in pediatric DCM and its relationship to ACV outcome.	Presence of two of the four criteria: ferritin < 20 µg/liter, iron < 9 µmol/liter, transferrin > 3 g/ liter, or TSAT < 15%.	ACV is defined as the need for MCS implantation, HT, or death.	single-center, retrospective observational cohort	47	Children with ID had significantly less freedom from the ACV outcome at 1-year (54% ± 10%), 2-years (45 ± 10%), and 5-years (37% ± 11%) than those without (p = 0.011). ID was a significant predictor of the ACV (HR 3.84 (95% CI 1.27, 11.59), P=0.017.
Newland, 2024 (Newland et al., 2024)	Seattle, Washington, USA	Assess the prevalence of ID and anemia in pediatric HT recipients after one year of HT.	- Serum ferritin <30 ng/mL (1) - Serum ferritin <30 ng/mL and TSAT < 20% (2)	Presence of ID (including the proportion based on definitions 1 and 2)	retrospective cross-sectional	115	Considering definition 1, ID prevalence was 46%. Considering definition 2, ID prevalence was 27%.

Notes: ACV, adverse cardiovascular; DCM, dilated cardiomyopathy; HF, heart failure; HT, heart transplant; ID, iron deficiency; IS, iron sufficient; MCS, mechanical circulatory support; OR, odds ratio; TSAT, transferrin saturation; VAD, ventricular assist device. For ferritin level (ng/mL = µg/liter), for iron level (9 µmol/liter = 50 mg/dL), for transferrin (300 ng/mL = transferrin > 3 g/ liter)

Table 2: *Summary of included studies' characteristics.*

One additional study, not captured in the systematic search strategy, was also included in this review. (Higgins et al., 2017) This paper was identified through reference screening during the full-text review process of included articles. Therefore, the total number of studies included is five. (Higgins et al., 2017; Luxford et al., 2024; Newland et al., 2024; Phillips et al., 2023; Puri et al., 2020) The study selection process is displayed in Figure 1, including the reason for excluding 7 reports. While both prospective and retrospective studies were eligible for inclusion, no prospective studies met all criteria, particularly the requirement to report both ID and ACV outcomes in individuals under 21. As such, all included studies were retrospective in design. The titles and authors of the articles excluded after full-text review are provided in Supplementary Information 3. (Haddaway et al., 2022)

Study Characteristics

All five studies (N=344) included in this systematic review used a retrospective single center design and provided ID prevalence data, which was included in the weighted mean prevalence analysis. Data from three studies (N=201) reporting ACV frequency by ID status were used to estimate the OR, 95% CI, and the pooled effect of ID as a risk factor for ACV. (Luxford et al., 2024; Phillips et al., 2023; Puri et al., 2020) The two studies excluded from the pooled effect analysis were Newland et al., which did not assess ACV occurrence, and Higgins et al., which reported deaths and MCS implementation but did not stratify by ID status. (Higgins et al., 2017; Newland et al., 2024) A summary of the included studies and their main findings can be found in Table 2.

One report included individuals under 18 years old, two included participants under 21 years old, and two included patients aged 1–21 years old. The availability of iron studies was an inclusion criterion for all studies, with the proportion of pediatric HF patients who were followed in each center and had iron studies available ranging from 34% to 60% in three reports. Two studies did not describe the total number of patients, making it impossible to calculate the proportion of iron studies available in these cases.

Levels of TSAT were available in all studies, four studies described ferritin levels, and two studies also had iron and transferrin levels available. The thresholds for ID definition varied among the studies. Ferritin levels ranged from less than 20 μg/liter to less than 100 μg/liter, while TSAT thresholds ranged from less than 15% to less than 20% for ID categorization. Additionally, iron and transferrin levels were

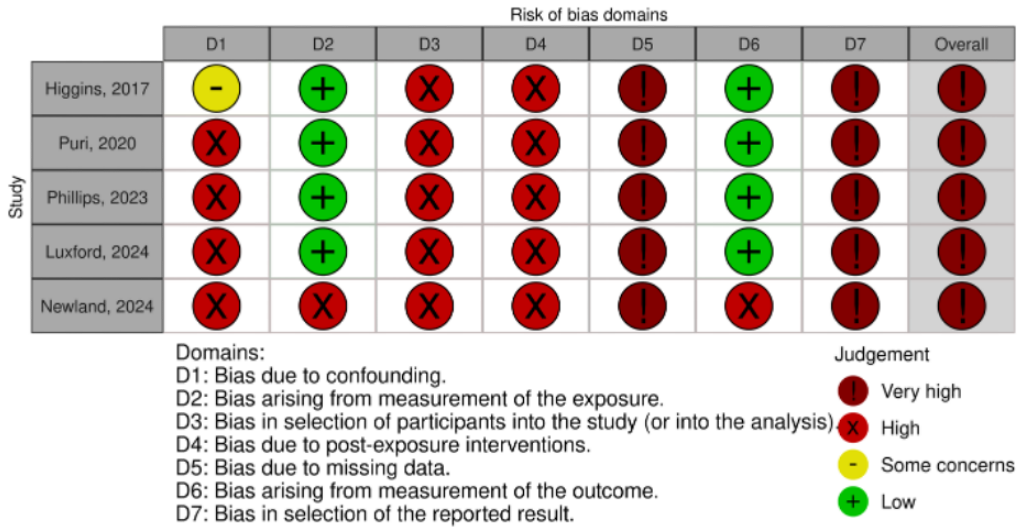

Figure 2: *ROBINS-E summary diagram for the included studies.*

considered in two studies. All authors categorized their study population as ID, iron sufficiency (IS), or iron replete. However, Phillips also included an "iron indeterminate" category (N=21), which was excluded from the analysis of this systematic review.

Sex distribution was available in all five studies, but data specific to ID/IS was available in only three reports, and no information on the rate of ACV by sex was reported. Race and ethnicity were labeled as "race/ethnicity" in two studies, with two studies presenting no information on race or ethnicity distribution. One manuscript described the frequency and proportion of "Aboriginal/Torres Strait Islander" as a categorical variable but did not specify whether it referred to race or ethnic group. The median follow-up time ranged from 6 months to 4.5 years. For full data extraction, please see Supplementary Information 4.

Risk of Bias in Studies

Overall, the included studies demonstrated poor methodological quality, as described in Figure 2. All studies were single-center retrospective, with participant selection closely related to the availability of iron studies and enrollment in a center for advanced pediatric HF management. This raises concerns about selection bias and missing data bias, affecting the generalizability of the findings.

Iron studies were not available for all patients with heart disease, and disease severity may have influenced clinicians' decisions to perform iron testing, potentially affecting the association between ID and ACV. Therefore, disease severity may confound the association of ID with subsequent ACV. Additionally, potential confounders like socio-economic status were not evaluated, and small sample sizes limited the analysis of variables such as race, sex, age, and the presence or absence of CHD. The reported results are also concerning due to multiple analyses within the same report and a lack of a pre-specified data analysis plan, which increases the risk of false-positive associations due to increased Type I error.

Study Description – Narrative Synthesis

ACV Outcomes

Taking into consideration the three studies with available information on ACV stratified by ID, two studies identified ID as a risk factor for ACV in pediatric patients with heart disease. (Luxford et al., 2024; Puri et al., 2020) On the other hand, one study did not show a significant effect of ID on clinical outcomes in this population. (Phillips et al., 2023)

Puri et al. analyzed data from 107 patients with either biventricular or single-ventricle heart disease. They found that ID significantly increased the odds of experiencing ACV events within six months, reporting an OR of 6.9 (95% CI 2.0, 24.1) for biventricular disease and OR 8.1 (95% CI 1.5, 42.3) for single-ventricle disease. ID-exposed patients also had a significantly higher cumulative length of hospital stay compared to those without ID (70% vs. 10% for biventricular and 65% vs. 2% for single-ventricle disease; p=0.001 for both). (Puri et al., 2020)

Phillips et al. assessed ID as a risk factor for ACV outcomes in children with HF induced by DCM. In

Author and Date	ID Definition	ID Prevalence (%)
Higgins, 2017	Ferritin <100 ng/mL alone or a ferritin 100 to 300 ng/ ml and TSAT <20%.	96.4
Puri, 2020	Presence of two of the four criteria: serum iron <50 mg/dL, serum ferritin <20 ng/mL, transferrin >300 ng/mL, and TSAT <15%.	56.1
Phillips, 2023	TSAT <20%	70.1
Luxford, 2024	Presence of two of the four criteria: ferritin < 20 µg/liter, iron < 9 µmol/liter, transferrin > 3 g/ liter, or TSAT < 15%.	61.7
Newland, 2024	- Serum ferritin <30 ng/mL (1) - Serum ferritin <30 ng/mL and TSAT < 20% (2)	46.1 (1) 26.1 (2)

Notes: ID, iron deficiency; TSAT, transferrin saturation. For ferritin level (ng/mL = µg/liter), for iron level (9 µmol/liter = 50 mg/dL), for transferrin (300 ng/mL = transferrin > 3 g/ liter)

Table 3: *ID prevalence for each study included in this review.*

a group of 47 individuals, ID was not associated with ACV outcome with an HR of 1.36 (95% CI 0.61, 3.04). The researchers also explored the association between ID and death, listing on the transplant registry, or VAD placement, finding no significant association. (Phillips et al., 2023)

Luxford et al. investigated ID as a risk factor for ACV in 47 children with DCM. In this cohort, ID was associated with ACV outcome represented by the HR 3.84 (95% CI 1.27, 11.59), P=0.017 in a univariate analysis. In this analysis, the increased risk over time was nearly fourfold in the group exposed to ID. Additionally, the median cumulative length of stay at six months follow-up was higher in the group exposed to ID compared with those with IS (14.7% vs. 1.1%, P=0.002). (Luxford et al., 2024)

Prevalence of ID

The prevalence of ID in children with heart disease ranged from 46.1% to 96.4% across the five studies reviewed. Under Newland's stricter criteria, the prevalence of ID ranged from 26.1% to 96.4%. The variation in the range of ID prevalence among the included studies is largely due to differences in the definition of ID, as described in Table 3.

Meta-analysis

Of the five studies included, three reported data on adverse cardiovascular outcomes (Phillips, Luxford, and Puri). These were included in the meta-analysis. The remaining two studies (Higgins and Newland) did not report ACV outcomes and were therefore considered only in the prevalence analysis.

ACV Outcomes: Primary Outcome

In the three studies with available information on the number of ACV outcomes by ID exposure, Phillips and Luxford used time-to-event analysis, estimating HR, to assess the risk over time of developing ACV, comparing patients exposed to ID with those not exposed. Puri used logistic regression and calculated OR to investigate the association between ID and ACV outcomes in the pediatric population. (Luxford et al., 2024; Phillips et al., 2023; Puri et al., 2020) The estimated OR, 95% CI, and P-values for each study using raw frequencies are reported in Table 4. The risk of bias was very high for all three studies included in this synthesis.

When conducting a meta-analysis of three studies that provided data on the number of ACV outcomes in participants under 21 years old exposed and non-exposed to ID, a random-effects model revealed a significant increase in the odds of developing ACV in the exposed group compared to the non-exposed group (OR 4.44, 95% CI 2.03–9.71, P < 0.001), as shown in the forest plot (Figure 3). Heterogeneity was low at 16.25%, and the Q statistic was not significant, although the limited number of studies might have impacted the power to detect statistical heterogeneity. The funnel plot represents the graphical representation of publication bias. It demonstrated the distribution of the 3 studies; the interpretability of it is limited due to the number of studies (Figure 4). The Stata code used for these calculations is detailed in Supplementary Information 5. The subgroup analysis planned to assess the robustness of the main results, and potential changes in the main effect by sex, type of heart disease, presence of missing exposure data, study quality, level of bias, and study design were not completed due to the limited number of studies identified.

Author and Year	Sample Size	Odds Ratio and 95% CI	P-value
Puri, 2020	107	5.83 (2.50, 13.61)	<0.001
Phillips, 2023	47	2.00 (0.54, 7.39)	0.298
Luxford, 2024	47	8.95 (1.03, 77.37)	0.046

Note: Estimated odds ratios, confidence intervals (CIs), and P-values were derived from logistic regression analyses using raw frequencies from each study.

Table 4: *Predictor of adverse cardiovascular events in pediatric patients with heart disease.*

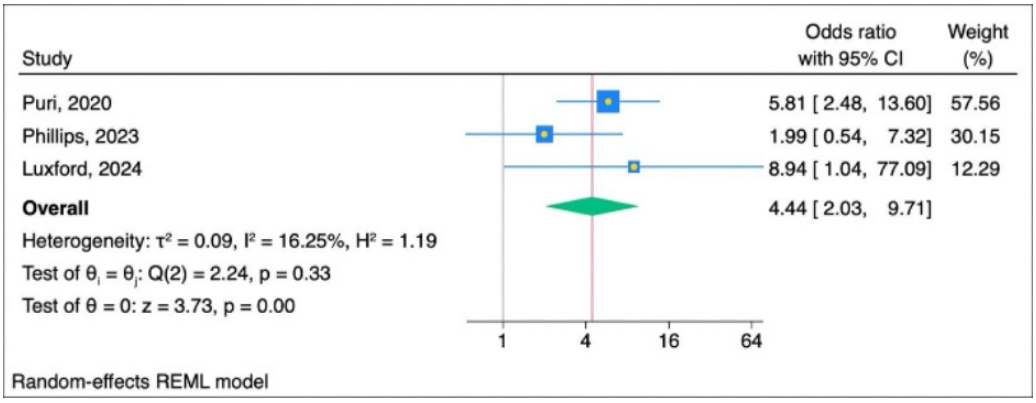

Figure 3: *Forest plot for random effect analysis with ID as risk factor for ACV outcome.*

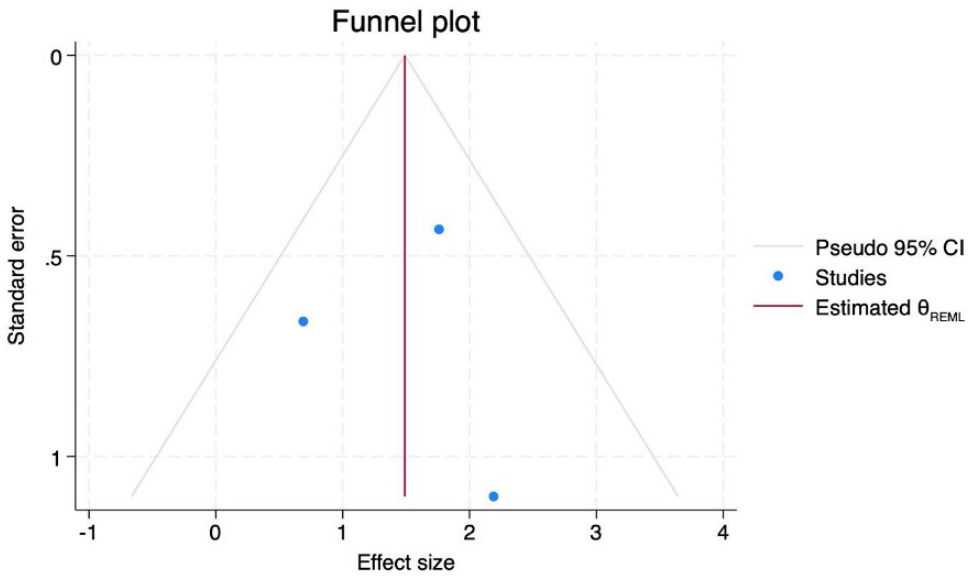

Figure 4: *Funnel plot for the three studies on ID and ACV outcomes in pediatric patients with heart failure.*

The weighted average prevalence of ID among these studies is 58.7% (95% CI: 53.7, 63.7). Applying the more stringent definition used by Newland et al., the weighted average prevalence is 52.0% (95% CI: 47.3, 56.8). When testing the secondary hypothesis to assess if ID prevalence in this sample was different from 38.4%, both prevalences of 58.7% and 52% were significantly different ($z=7.75$ and $z=5.2$, both $p<0.001$). Both results suggest that the observed prevalence is unlikely to be due to chance.

Discussion

Summary

This systematic review summarized evidence on ID as a risk factor for ACV in individuals under 21 with heart disease, indicating that ID is highly prevalent. ID was associated with a 4-fold increase in ACV odds based on a meta-analysis of three studies. While the effect size is significant, the wide CI suggests some heterogeneity. Notably, when estimating the OR across the three studies, all individual ORs fall within the CI of the pooled effect. Although the I^2 statistic is relatively low (16.25%) and the Q test does not meet the statistically significant threshold for heterogeneity, the small number of studies limits the power to detect differences, potentially leading to a type II error. The methodological quality of the studies was poor, with high risks of bias related to selection bias, missing data, multiple analyses reported, and inadequate confounder analysis.

ID Prevalence

The prevalence of ID is considerably high in this population, with a weighted average prevalence of 58.7% among the five studies. This value is higher than previously published prevalences in most studies including adults with HF. In two prospective studies including adult population, ID was identified in 37% of 546 ambulatory HF patients and in 42.5% of 1,198 patients from office-based cardiology practices. (Jankowska et al., 2010; von Haehling et al., 2017). In the pediatric field, the prevalence found in this review is also higher compared to the prevalence described in a nationally representative survey from the US, where 38.6% of participants had ID. (Weyand et al., 2023) In a cohort study of 437 children with chronic kidney disease, the prevalence of ID was 24.4%. (Lee et al., 2019)

While the 38.6% ID prevalence reported by Weyand et al. in healthy adolescents provides a useful reference point, it may not be directly comparable to the hospitalized pediatric heart disease population studied here, which likely represents a group with greater disease severity and inflammation, factors known to influence iron metabolism. In addition, the higher prevalence found in this review may be linked to the severity of pediatric heart disease, as most patients analyzed were hospitalized, unlike adults with HF who were recruited from ambulatory settings. Additionally, the inclusion criteria in all five reports were based on the availability of iron studies, likely driven by clinical suspicion of ID. This may have led to a higher observed prevalence, reflecting a subgroup where ID was suspected rather than the broader population under 21 with heart disease.

It is important to note that the reported prevalence is derived solely from studies included based on the primary outcome (ACV). Consequently, studies focusing exclusively on ID prevalence, without examining ACV, were excluded from the analysis. This methodological approach may have limited the comprehensiveness of prevalence data, but aligns with the study's aim to evaluate the relationship between ID and ACV.

Effect Size of ID as Risk Factor for ACV Outcome

The strength of the association found in this meta-analysis between ID and ACV outcome in pediatric patients with heart disease was OR 4.44, indicating that individuals exposed to ID presented roughly 4 times higher odds to develop the outcome in comparison with those not exposed, which is a large effect size. In contrast, two large studies in adults with HF have shown a smaller effect size, with an adjusted HR of 1.58 reported by Jankowska et al. and an adjusted HR of 1.42 by Klip and colleagues. (Jankowska et al., 2010; Klip et al., 2013)

In both cases, the models were adjusted for clinical factors such as age, sex, functional class, systolic function, cardiac natriuretic peptides, diabetes, renal function, and inflammatory markers. The larger effect size in this review compared to previous studies in adults with HF may be related to the lack of adjustment for confounders, such as sex, race, socioeconomic status, and markers of disease severity like natriuretic peptides, ventricular dysfunction, and functional class. Biologically, younger patients may be more susceptible to ID due to its close link with somatic growth and neurological development, potentially amplifying the effect size. Clinically, the higher mortality rates in pediatric HF patients suggest greater disease severity in children compared to adults. (Amdani et al., 2022)

This may have contributed to the larger effect size found in this review compared to previous data in adults. While ID appears to have a more pronounced effect on pediatric patients with heart disease,

clinicians must consider the broader clinical context when making treatment decisions. This includes evaluating the severity of disease, accounting for potential confounders, and tailoring interventions to the individual needs of the patient.

The broad CI found in this review, ranging from 2.03 to 9.71, is notable and may reflect the limited number of individuals included in the analysis and the heterogeneity of the populations, which included both CHD and cardiomyopathy. Although these conditions account for nearly all heart disease in children, their etiologies differ significantly. Cardiomyopathy may result from genetic diseases associated with myocardial dilation and dysfunction or from acquired infectious diseases such as myocarditis and acute rheumatic fever. (Kim et al., 2023; Rath & Weintraub, 2021) Conversely, CHD includes a wide range of conditions, from simple septal defects to complex single-ventricle defects where repair is not possible. (Harrison et al., 2022) This diversity highlights the heterogeneity of pediatric heart disease and presents challenges when studying this population.

Discrepancies in Findings Across Individual Studies

Puri's and Luxford's studies identified ID as a risk factor for ACV in pediatric patients with heart disease. (Luxford et al., 2024; Puri et al., 2020) On the other hand, Phillips and colleagues did not show a significant effect of ID on clinical outcomes in this population. (Phillips et al., 2023) The discrepancies among these findings likely stem from multiple factors, including differences in how ID was defined and variations in disease severity, which can lead to confounding by severity and exposure bias.

Firstly, studies use different definitions for ID. Puri et al. and Luxford et al. defined ID using multiple iron studies, as recommended by the National Health and Nutrition Examination Survey. Conversely, Phillips et al. relied solely on TSAT below 20% as the criterion for ID, regardless of ferritin or iron levels. Importantly, in Phillips' study, the mean ferritin level in the ID group was 62.6 μg/liter, which does not meet the ID threshold used by the other two studies, where the ferritin level threshold was < 20 μg/liter.

The second factor is the heterogeneity in disease severity across the studies. In Phillips' study, the severity of heart disease appeared similarly high in both the ID and IS groups, with comparable proportions of inpatient settings (70% vs. 64%, P=0.716) in both groups. In Luxford's study, the proportion of inpatients was significantly higher in the ID group (86.2% vs. 50%, P=0.010), as was the proportion of patients with moderate or more mitral regurgitation (51.7% vs. 22.2%, P=0.045), and the N-terminal pro-brain natriuretic peptide level was also higher in the ID group (1590.5 vs. 112.6, P=0.001). In Puri's study, brain natriuretic peptide levels, another marker associated with adverse cardiovascular events in this population, were higher in patients with ID (1950 vs. 788, P<0.001).

These factors suggest that the ID group in the studies by Puri and Luxford might have had more severe disease. Consequently, disease severity, rather than ID, might be associated with ACV, and in support of this possible interaction, Puri and Luxford's studies found statistically and clinically significant differences in hospitalization rates, mitral regurgitation, and cardiac natriuretic peptide levels between groups. In contrast, Phillips' study found no statistically significant differences in severity markers between the ID and IS groups, which may explain the lack of association between ID and ACV.

Implications for Public Health and Clinical Practice

The high prevalence of ID in pediatric heart disease patients and the increased odds of ACV events in those with heart disease and ID highlight the need for early diagnosis. Community pediatricians and specialty care institutions that manage children with heart disease should improve their awareness of ID in these children. Additional guidelines integrating ID screening into routine clinical practice for this and other high-risk populations should be considered. Since ID diagnosis is cost-effective and scalable, broad application may be feasible. While subgroup variations weren't explored, policies should address socioeconomic disparities and target high-risk sociodemographic groups. Early recognition of ID, along with interventions like education and awareness programs, dietary improvements, and timely treatment, may reduce the future secondary impacts of heart disease in children.

Iron supplementation is an established intervention for adults with HF, with intravenous iron shown to improve exercise capacity, quality of life, and potentially reduce hospitalizations for HF. (Graham et al., 2023) In pediatric patients, oral iron replacement is the first-line treatment for those presenting with ID, offering a relatively inexpensive approach to address this nutritional deficiency. However, a retrospective cohort study of 20 pediatric patients, who had iron levels measured before and after 3 months of iron supplementation, found that 55% of patients remained with ID despite of oral iron

therapy. (Puri et al., 2022) Although this systematic review supports ID as a risk factor for ACV outcome in pediatric patients with heart disease, oral iron replacement may not necessarily reduce the risk of ACV events in this group of patients.

Strengths

The strengths of this review include the systematic approach used to review the literature, select reports for analysis, and assess the risk of bias. The use of ACV as an outcome, a hard clinical outcome widely used in pediatric cardiology, is also an advantage of this review. The estimation of OR in the three studies that presented the number of ACV outcomes by iron status using logistic regression models allowed the calculation of the pooled effect, pioneering this analysis in the pediatric heart disease population. Additionally, the review highlights the importance of ID as a potentially modifiable risk factor for ACV outcomes in this population.

Limitations

This systematic review has several limitations. Study selection and data extraction were performed by the first author, which may have limited the number of included studies due to individual judgment and increased the risk of missing relevant data; however, all findings were carefully discussed within the research team, and data collection followed the prespecified plan. In addition, our review was restricted to English-language publications and did not include grey literature, which may have introduced language and publication bias and limited the comprehensiveness of the evidence base. The risk of bias is high across all five studies, which may affect the validity and interpretation of the results.

All studies were conducted in the US and Australia, limiting the generalizability to other populations, especially in low- to middle-income countries like Latin America, Asia, and Africa, where ID and anemia are significant public health concerns. (MacPhail, 2001; Mantadakis et al., 2020)

All studies were retrospective, single-center investigations involving patients already enrolled in advanced pediatric HF programs, raising concerns about selection bias and limiting generalizability. Additionally, the lack of confounder assessment and the limited sample sizes further complicate the findings, making it difficult to determine whether the suggested link between ID and ACV in pediatric patients is valid or if it might be influenced by confounding bias. Given that race, ethnicity, and socioeconomic status are established risk factors in this population and were not included in the analysis, the validity of the evidence is questionable. (Amdani et al., 2023; Judge et al., 2023)

Lower socioeconomic status is often associated with limited access to nutritious foods, increasing the risk of ID due to dietary insufficiency. (Bayoumi et al., 2020; Zarnowiecki et al., 2014) It can also impact the timing of diagnosis, access to advanced HF therapies, and adherence to medical follow-up, which are critical determinants of ACV in pediatric heart disease. (Bucholz et al., 2020; Greenwell et al., 2024) Additionally, age and the presence of CHD are well-established risk factors for ACV in pediatric patients. (Lasa et al., 2020) As a consequence, the lack of confounder analysis raises concerns about whether the observed association between ID and ACV is valid or influenced by these known confounding variables. Although developmental differences in iron metabolism may exist between younger children and adolescents, subgroup analysis by age was not feasible due to a lack of consistent age-stratified data across studies and small sample sizes.

None of the studies had a pre-specified analysis plan, and the reporting of multiple outcome assessments increased the risk of false-positive associations. Regarding publication bias assessment, the funnel plot's interpretability is limited due to the lack of power in an analysis with fewer than 10 studies. With only three studies meeting the inclusion criteria, publication bias is a concern. This may be due to journals favoring studies on more common conditions like hypertension and myocardial infarction over those focused on cardiovascular disease in children. The small number of studies included also limited the subgroup analysis planned in the methodology plan.

The variation in ID definitions across the studies complicates the classification of patients, limits our ability to conduct subgroup or sensitivity analyses, and may lead to misclassification bias, potentially distorting the observed relationship between ID and ACV. Establishing a standardized definition of ID in pediatric patients is essential for improving evidence, supporting universal screening, and guiding future studies on iron replacement therapy in children with heart disease.

Furthermore, while all effect estimates in the meta-analysis were expressed as ORs, two of the original studies reported HRs, which capture time-to-event relationships. To maintain consistency, we calculated ORs using raw frequencies. However, this approach may oversimplify the temporal dimension of outcomes and limit comparability.

Future meta-analyses with access to individual participant time-to-event data would permit more robust pooled HR estimates.

Conclusion

ID is highly prevalent among pediatric patients with heart disease. Evidence from this systematic review and meta-analysis suggests that ID is a risk factor for ACV outcomes, with patients exposed to ID having four-fold higher odds of developing ACV compared to those without ID. However, the very high risk of bias across the included studies limits the generalizability of these findings. Despite these limitations, this synthesis provides valuable insights for shaping prospective research agendas and highlights the need to consider ID in clinical screening strategies for children with heart disease. Future research should focus on patient-centered outcomes, employ rigorous methodology, and broad inclusion criteria to enhance the quality and generalizability of findings. Involving patients, families, and key stakeholders in study planning, execution, and reporting will be crucial for tailoring future projects to address the needs of those experiencing the disease.

Author's Contributions

Karla L. Loss: literature review, study conception and design, data collection, analysis and interpretation of results, and manuscript preparation and final review and editing. Erica V. Stelmaszewski: literature review, study conception and design, data collection, writing – review & editing. Jennifer Su: writing – review & editing, methodology, conceptualization. Gustavo C. Pinasco: writing – review & editing, methodology. Emma Beard: writing – review & editing, supervision, methodology, conceptualization. Paul Kantor: writing – conceptualization, supervision, methodology, review & editing.

Supplementary Materials

PRISMA 2020 main checklist; search terms and strategy; complete data extraction from the included studies.

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Conflicts of Interest

The authors declare no conflict of interest.

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