

A history of iron deficiency is associated with primary and chronic pain disorders in children and adolescents, and in adults





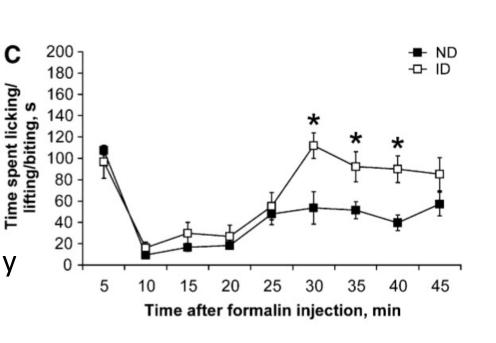
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Background

- The authors have had long-standing research interests in restless legs syndrome which is causally influenced by iron deficiency and is associated with multiple pain disorders.
- We have included a history of iron deficiency in our studies on primary pain syndromes and chronic pain in children, adolescents and young adults.
- Previously, the only published studies reporting association between iron deficiency and pain was for single conditions, especially migraine and fibromyalgia.
- Iron deficiency sensitises mice to acute pain stimuli and formalin-induced nociception.

The present mouse model of nutritional iron deficiency is associated with a reduced pain threshold (hotplate test) and, subsequently as shown here, heightened pain sensation after formalin injection.



Dowling P, Klinker F, Amaya F, Paulus W, Liebetanz D. J Nutr. 2009;139(11):2087-92.

Rationale for using history of iron deficiency

- Brain imaging for iron deficiency is limited to research in low numbers.
- Iron biomarkers such as ferritin would not inform about iron deficiency in infancy (39% of paediatric responders with iron deficiency) nor after treatment.
- History of iron deficiency, doctor confirmed, was appropriate for epidemiological research by questionnaire.

Objectives

- Our objective is to highlight the associations between a history of iron deficiency in 3 studies in children, adolescents, and young adults, and now to present confirmation of the association between a history of iron deficiency and multiple pain conditions in adults.
- We consider whether iron deficiency association with pain is causal. Potential mechanisms are currently being reviewed.

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Study 1

In search of risk factors for chronic pain in adolescents: a case-control study of childhood and parental associations.

Coenders A, Chapman C, Hannaford P, Jaaniste T, Qiu W, Anderson D, Glogauer M, Goodison-Farnsworth E, McCormick M, Champion D. *J Pain Res* 2014;7:175-183.

- Our case—control study involved 101 adolescents aged 10–18 years. Cases were 45 patients of the Chronic Pain Clinic at Sydney Children's Hospital with diverse chronic pain disorders. Controls consisted of 56 adolescent volunteers who did not have chronic pain.
- A history of iron deficiency was one of 17 potential associations tested.
- A history of iron deficiency was obtained in 24.4 % of cases and 7.3% of pain free controls [OR 4.1, 95%CI 1.2-14.0, p = 0.04).

Study 2

Common Pediatric Pain Disorders and Their Clinical Associations

Donnelly TJ, Bott A, Bui M, Goh S, Jaaniste T, Chapman C, Crawford M, Hopper JL, Champion D. Clin J Pain. 2017;33(12):1131-1140.

Association between each pain disorder & restless legs syndrome (outcome) and iron deficiency (predictor), adjusted for age and gender whenever significant. GEE was used as estimating method.

Outcome	OR	p-value	95%CI
Migraine	2.18*	<mark>0.009</mark>	1.22-3.92
Headache	1.39**	0.210	0.83-2.32
Recurrent abdominal pain	2.36*	<mark>0.0002</mark>	1.49-3.74
Persistent/chronic pain (diverse)	4.59*	7.0x10 ⁻⁹	2.74-7.68
Growing pains selective	1.22	0.467	0.72-2.07
RLS-Painless	5.43*	5.6x10 ⁻¹⁰	3.18-9.27
RLS-Painful	2.14*	<mark>0.022</mark>	1.12-4.11

Adjusted for *age and **age and gender.

Study 3

Primary dysmenorrhoea in adolescents and young women: A twin family study of maternal transmission, genetic influence and associations

Aouad P, Bui M, Sarraf S, Donnelly T, Chen Y, Jaaniste T, Eden J, Champion D. ANZJOG 2022 (under review)

Univariate association between each dysmenorrhoea measure (outcome) and iron deficiency (predictor), adjusted for age.

	Maximum Pain Intensity	Average Pain Intensity	Pain Interference	RDSSS [†]
	(N = 202)	(N = 203)	(N = 203)	(N = 206)
Iron deficiency	1.60 ± 0.56**	1.26 ± 0.52*	-0.68 ± 5.10	1.43 ± 1.87

 β = estimated regression coefficient; s.e = standard error; p-value *<0.05, **<0.01. †RDSS: Retrospective dysmenorrhoea secondary symptom scale. For Pain Intensity and Average Pain Intensity, those predictors that were significant in the univariate association were considered in the multivariate analysis and remained significant. RLS-Painless was the other main multivariate association with dysmenorrhoea measures (all 4).

Confirmatory study in adults

Association analyses of questionnaire data from adult responders (twins, spouses & offspring) to a twin family study of painless and painful restless legs syndrome

Association between history of iron deficiency (as predictor) and pain conditions

Pain conditions as statistical outcomes	All responders (male and female)				
	N	OR	р	95% CI	
Migraine	1327	1.04^{1}	0.81	0.75-1.43	
Headache (recurrent)	1327	1.12 ¹	0.44	0.84-1.49	
Recurrent abdominal pain	1327	1.47^{1}	0.02	1.05-2.05	
Chronic pain disorders (diverse)	1327	2.05 ²	<mark>0.01</mark>	1.17-3.60	
Growing pains	1236	1.49^{2}	0.18	0.83-2.65	
Arthritis	752	0.28	0.16	0.05-1.64	
Dysmenorrhoea (Females)	838	1.55	<mark>0.03</mark>	1.05-2.29	
Chronic Spinal Pain	1266	1.71 ²	<mark>0.02</mark>	1.09-2.67	

Analyses were conducted using logistic regression, applying generalised estimating equations, adjusted for ¹gender, ²age and ³gender and age. Total 36.4% had a history of iron deficiency: 52.8% of females, 5.1% males.

Conclusions

Previously

- It was shown that induced iron deficiency in mice caused lower pain threshold and increased sensitivity.
- Iron deficiency had been reported in association with individual pain conditions, notably migraine and fibromyalgia.
- Iron deficiency is causally associated with restless legs syndrome which, in turn, is strongly associated with multiregional pain and with pain syndromes.

We have shown

- A history of iron deficiency, doctor confirmed, was associated in three studies in children, adolescents and in young women with multiple regional pain disorders and defined pain syndromes. There were indications also, especially in dysmenorrhea, that iron deficiency was associated with increased pain sensitivity.
- Similar associations have now been found in adults.

Cause-association considerations

 Application of the Bradford Hill criteria for likely causation in the association between iron deficiency and pain sensitivity and vulnerability leads to the conclusion:

A causal influence of iron deficiency on pain sensitivity and on vulnerability to pain regions and conditions is an appropriate hypothesis to be tested.