

Iron status has generally not been considered in the determination of sex-based hemoglobin reference intervals: A systematic review

I. Blydt-Hansen¹, V. Swarup², R. Thillaye-Kerr², R. Sampat², C. Bekdache², V. Giuliano³, T. Kishibe⁴, A. Weyand⁵, M. Crowther⁶, M. Wozniak, M. Fralick⁷, GH. Tang^{2,8} & M. Sholzberg^{2,8,9}

¹Department of Internal Medicine, University of British Columbia, Vancouver, BC, Canada; ²Hematology-Oncology Clinical Research Group, Division of Hematology-Oncology, St. Michael's Hospital, Toronto, Canada; ³Department of Internal Medicine, University of Toronto, Toronto, ON, Canada; ⁴Health Sciences Library, St. Michael's Hospital, Li Ka Shing Knowledge Institute, Toronto, Canada; ⁵Department of Pediatrics, University of Michigan Medical School, Michigan, United States of America; ⁶Department of Medicine, McMaster University, Hamilton, ON, Canada; ⁷Department of Medicine, Mount Sinai Hospital, Toronto, ON, Canada; ⁸Li Ka Shing Knowledge Institute, University of Toronto, Toronto, ON, Canada; ⁹Departments of Medicine, and Laboratory Medicine and Pathobiology, St Michael's Hospital, Toronto, ON, Canada

BACKGROUND

- Anemia is defined by the World Health Organization as a hemoglobin of <120 g/L for women and <130 g/L for men
- There is increasing awareness that these sex-based hemoglobin reference intervals (RIs) may be derived from studies that include populations at risk for iron deficiency
- We therefore conducted a systematic review to evaluate the existing literature on sex-based hemoglobin RIs to establish if healthy females without evidence of or risk factors for iron deficiency have a lower baseline hemoglobin than healthy males

OBJECTIVES

To determine if studies establishing sex-based hemoglobin reference intervals have considered iron deficiency and its associated risk factors.

METHODS

A systematic review was conducted using a database search from inception to July 2024:

- Search strategy:** A systematic review was conducted using comprehensive search of MEDLINE, EMBASE, CINAHL and Web of Science
- Articles included:** Studies establishing a sex-based mean hemoglobin or hemoglobin reference interval in a *healthy population*
- Study selection:** Studies conducted in a state of pathophysiology were excluded: bone marrow pathology, inflammation, red cell disorders, systemic illness, etc.
- Review process:** 2 primary reviewers and additional assistance at extraction stage. Clear adjudication process in the event of disagreement.

Quality of the included studies was determined a-priori and addressed the following parameters:

- Population Health:** Manner in which 'health' was defined and integration of iron deficiency assessment in study design
- CLSI:** Adherence to Clinical Laboratory Standards Institute (or NCCLS prior to 2005) guidelines for establishment of reference interval studies
- Methods applied and results reporting:** Methodological rigor and transparent reporting of results

RESULTS

Of the 7489 articles were generated from the search strategy, 295 articles met inclusion criteria and were analyzed. 138/295 articles sought to establish a hemoglobin RI. 157/295 established a mean hemoglobin within the study population. Of the articles that sought to establish an RI, 78 adhered to CLSI guidelines (57%). 47/295 articles excluded individuals with laboratory evidence of iron deficiency (16%). Ferritin was assessed in 107/295 articles (36%).

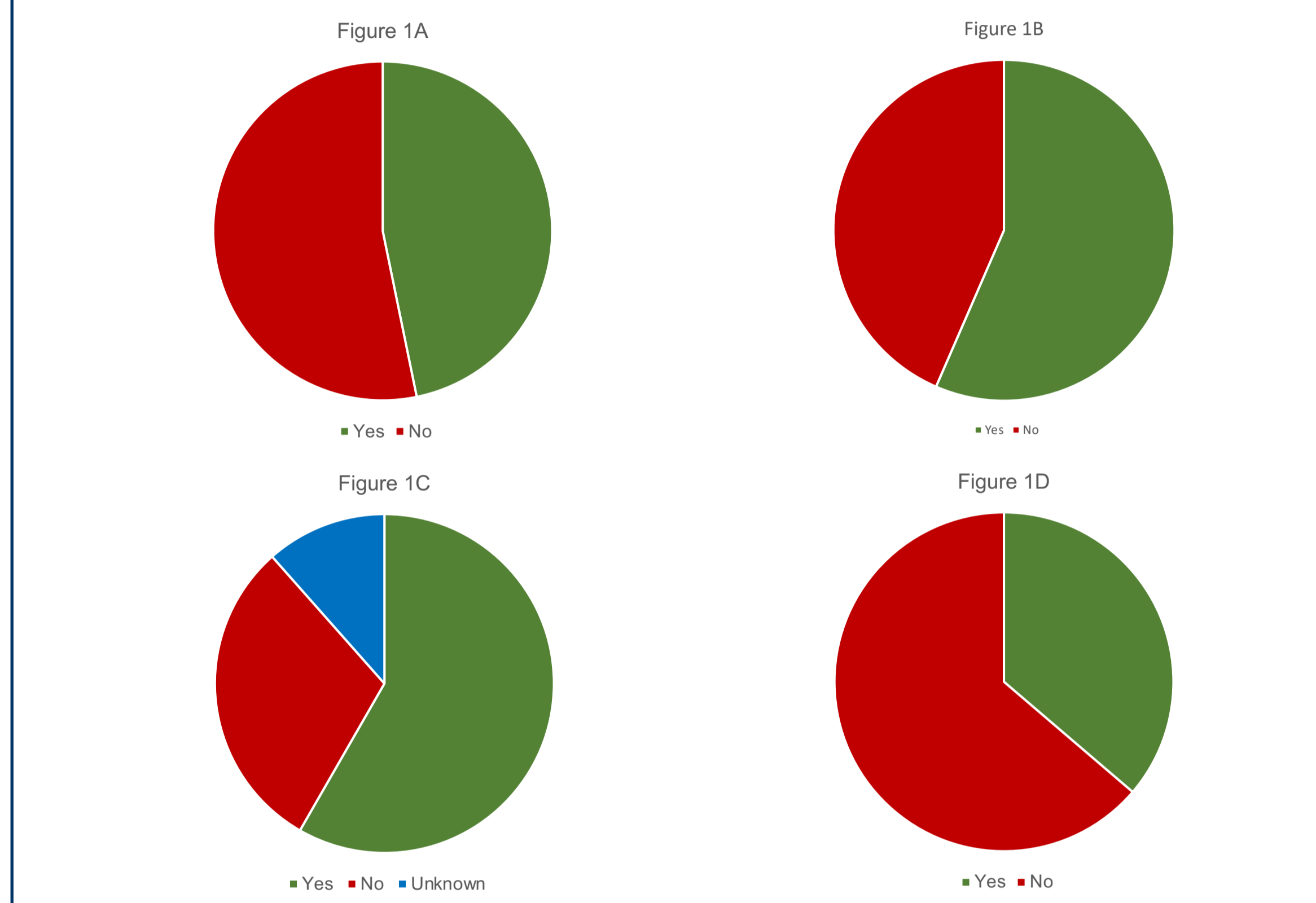


Figure 1. A) Number of studies that attempted to establish a reference interval (RI) B) Of the studies that established an RI, the number of studies that adhered to CLSI C) If individuals with known iron deficiency risk factors were excluded from the study D) Ferritin assessment in study population

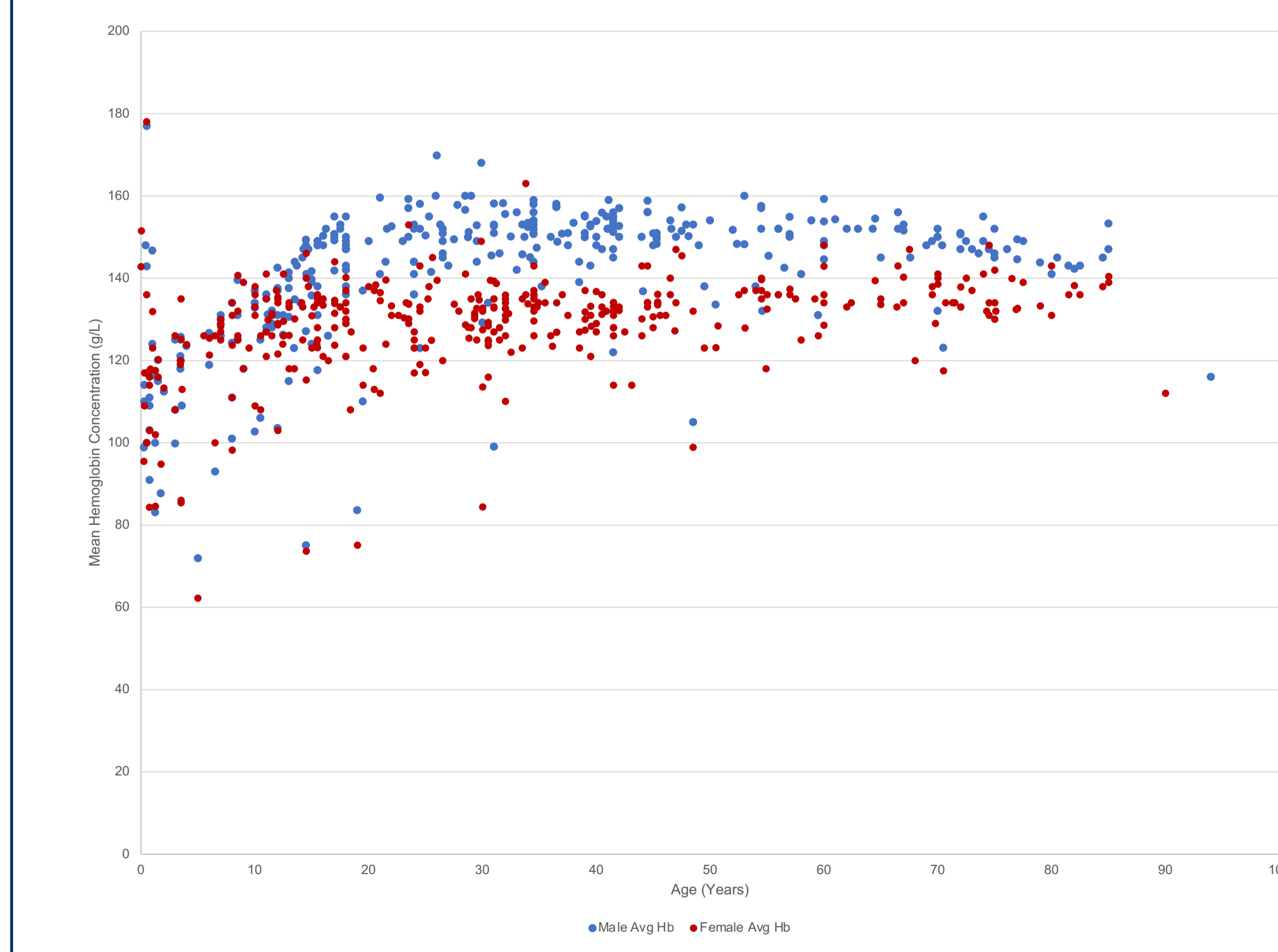


Figure 3. Mean hemoglobin (Hb) concentration (g/L) between females and males in studies that established an average Hb concentration within the study population.

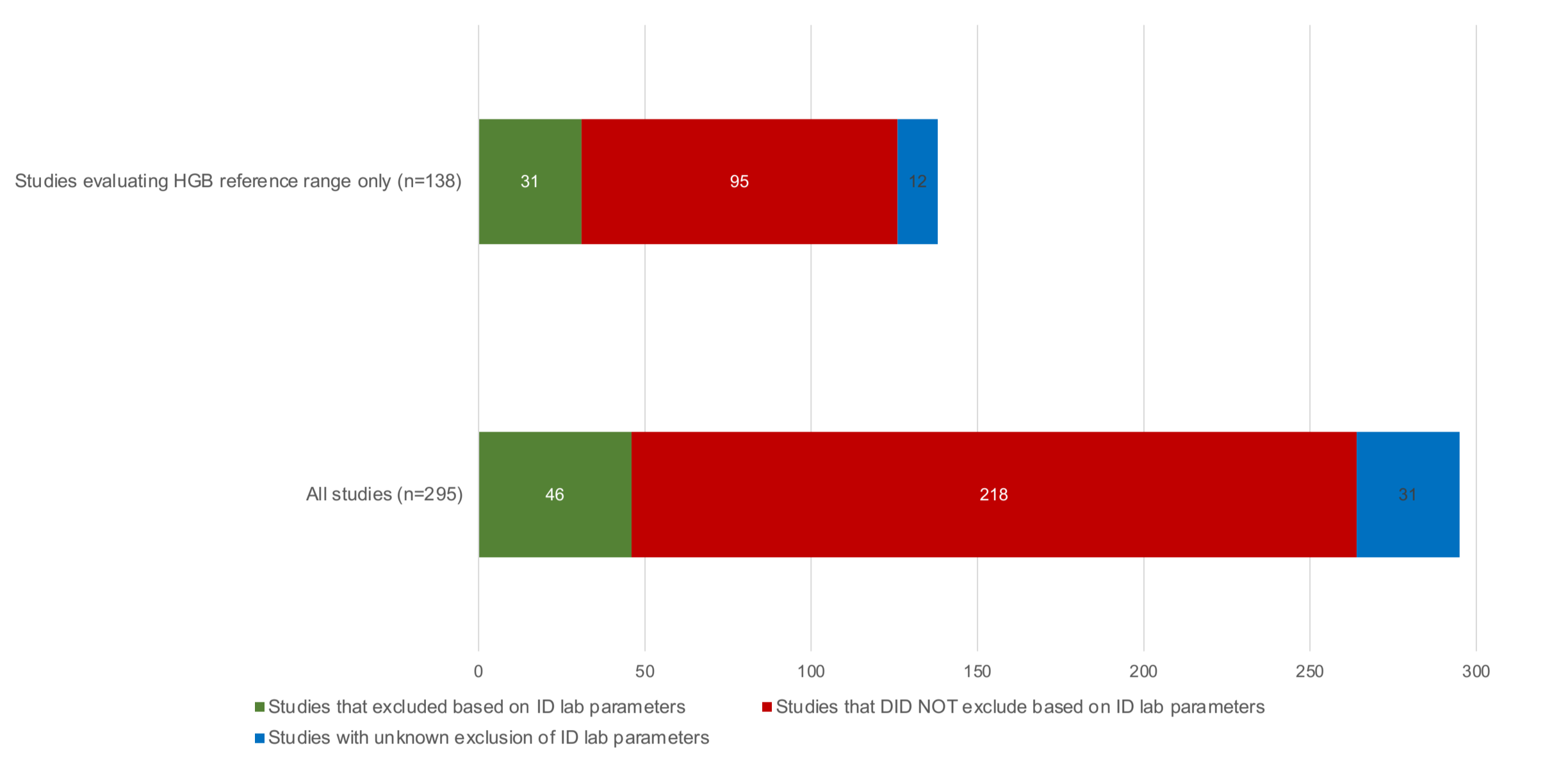


Figure 2. Number of studies that excluded participants based on iron-deficiency (ID) laboratory parameters and ones that did not.

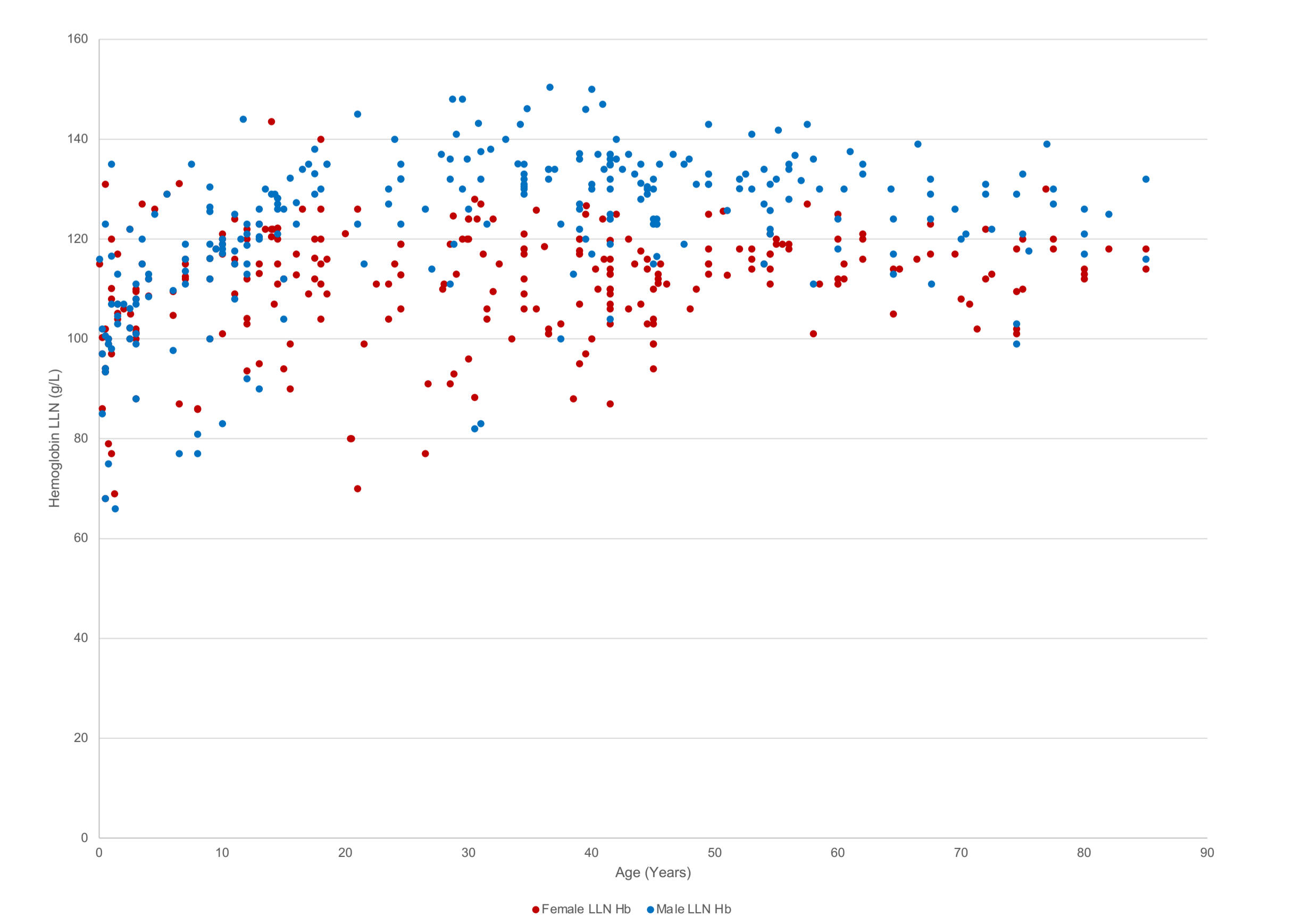


Figure 4. Lower limit of normal (LLN) hemoglobin (Hb) concentration (g/L) between females and males in studies that established a Hb reference interval within the study population.

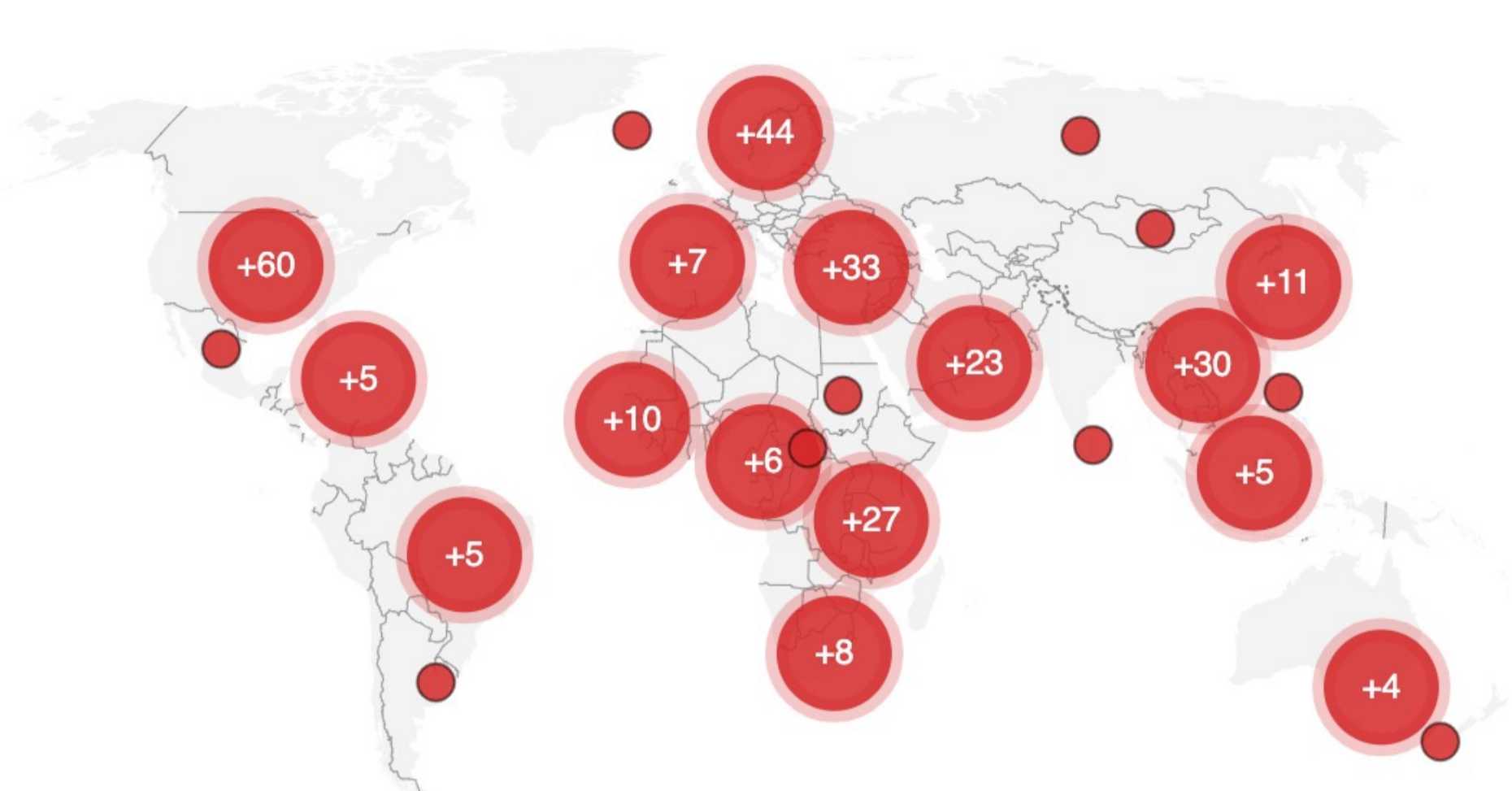


Figure 5. Geographic representation of articles included in the systematic review.

CONCLUSIONS

- This review demonstrates a systematic and extensive lack of consideration of iron deficiency and its associated risk factors when defining what constitutes a normal hemoglobin
 - Issue of healthy equity given the implications for women of reproductive age
- Iron deficiency prevalence leads to this having significant, widespread implications for under-diagnosis and treatment
 - Particularly relevant for individuals with bleeding disorders
- This systematic review identifies a significant structural issue in the literature and demonstrates the need for more definitive establishment of hemoglobin reference intervals in a hematologically healthy population

ACKNOWLEDGEMENTS

- Dr. Michelle Sholzberg**
- Vidushi Swarup
- Dr. Grace Tang
- Rowan Thillaye-Kerr, Rebecca Sampat, Carine Bekdache, Dr. Vanessa Giuliano
- Teruko Kishibe
- Dr. Angela Weyand, Dr. Mark Crowther, Dr. Michael Fralick, Dr. Miranda Wozniak

CONTACT INFORMATION

Ingrid Blydt-Hansen, PGY3
Ingrid.blydthansen@mail.utoronto.ca
 Department of Internal Medicine
 University of British Columbia