Iron status as a confounder in the gender gap in survival under extreme conditions

Joris R. Delanghe[a,1], Marijn M. Speeckaert[b], and Marc L. De Buyzere[b]

Zarulli et al. (1) report on male–female survival differences in populations of slaves and populations exposed to severe famines and epidemics. Although the facts are clear and convincing, attention should be paid to the role of iron as a confounder in explaining the gender-based mortality differences. Because iron is scanty in the biosphere, human populations in Europe and Africa have been selected based on iron conservation (2). In particular, Celtic, Viking, and Bantu populations have undergone an iron-driven genetic selection (2, 3). On the other hand, iron conservation makes populations more prone to siderophilic infections and vitamin C deficiency (4–6). Among famine victims, scurvy is a common cause of death (4). As women generally have smaller body iron stores compared with men, they are less prone to develop scurvy or infections with siderophilic microorganisms under extreme situations like those described in the Zarulli et al. (1) study (famines and epidemics). It is striking that all but one of the seven populations selected by Zarulli et al. are characterized by high allele frequencies of iron-conserving mutations [Q248H ferroportin and hemoglobin S (Liberia, Trinidad), HFE C282Y (Ireland, Iceland, and Sweden)] or suffering from siderophilic infections (dysenteria). In the case of Liberia, a high prevalence of hemoglobin S carriers (a condition associated with iron overload) is present, exceeding those of the neighboring countries (7). During the Irish famine, scurvy was a major cause of death, which has been linked to the extremely high HFE C282Y allele frequency in Ireland (4).

Except for the slave population of Trinidad, in all of the other cases described by Zarulli et al. (1), starvation, dysentery, and diarrhea are likely to have been major causes of death. Hereby, it is noteworthy to state that *Shigella*, enteropathogenic *Escherichia coli*, and *Entamoeba histolytica* (the main microorganisms involved in dysentery) are siderophilic microorganisms (8–10). Exposure of bacteria to members of the stress-associated catecholamine hormones, principally norepinephrine, has been demonstrated to increase both growth and production of virulence-related factors. Mutation of genes for enterobactin synthesis and uptake revealed an absolute requirement for enterobactin in norepinephrine-stimulated growth of *E. coli* O157:H7. In conditions of extreme stress, like the ones described by Zarulli et al. (1), the stress hormone norepinephrine promotes iron shuttling between transferrin molecules, thereby enabling the bacterial siderophore enterobactin to more readily acquire iron for growth (10). The stress-associated hormonal output may affect enterohemorrhagic *E. coli* pathogenicity (10).

The gender gap in life expectancy coincides with the gender gap in iron status and reduces after menopause, which further supports the role of iron in this respect. Next to social factors, genetic particularities affecting iron metabolism of populations at risk also might contribute to the explanation of the gender gap in survival.

1 Zarulli V, et al. (2018) Women live longer than men even during severe famines and epidemics. *Proc Natl Acad Sci USA* 115:E832–E840.
2 Delanghe JR, Speeckaert MM, De Buyzere ML (2016) The evolutionary adaptation of hemochromatosis associated mutations during the Neolithic. *Am J Phys Anthropol* 161:530–531.
3 Delanghe JR, et al. (2011) Vitamin C deficiency: More than just a nutritional disorder. *Genes Nutr* 6:341–346.
4 Delanghe JR, De Buyzere ML, Speeckaert MM, Langlois MR (2013) Genetic aspects of scurvy and the European famine of 1845–1848. *Nutrients* 5:3582–3588.
5 Kasvosve I, Speeckaert MM, Speeckaert R, Masukume G, Delanghe JR (2010) Haptoglobin polymorphism and infection. *Adv Clin Chem* 50:23–46.
6 Delanghe J, Speeckaert M, De Buyzere ML, Langlois M, Torck M (2012) Human plasma protein polymorphisms and the persistence of cultural diversity. *Proc Natl Acad Sci USA* 109:E2914.

[a]Department of Clinical Chemistry, Ghent University, B 9000 Ghent, Belgium; and [b]Department of Internal Medicine, Ghent University, B 9000 Ghent, Belgium

Author contributions: J.R.D., M.M.S., and M.L.D.B. designed research; J.R.D., M.M.S., and M.L.D.B. performed research; M.L.D.B. analyzed data; and J.R.D. and M.M.S. wrote the paper.

The authors declare no conflict of interest.

[1]To whom correspondence should be addressed. Email: joris.delanghe@ugent.be.

7 Neel JV, Robinson AR, Zuelzer WW, Livingstone FB, Sutton HE (1961) The frequency of elevations in the A and fetal hemoglobin fractions in the natives of Liberia and adjacent regions, with data on haptoglobin and transferrin types. *Am J Hum Genet* 13:262–278.
8 Wyckoff EE, Boulette ML, Payne SM (2009) Genetics and environmental regulation of *Shigella* iron transport systems. *Biometals* 22:43–51.
9 Hernández-Cuevas NA, Weber C, Hon CC, Guillen N (2014) Gene expression profiling in *Entamoeba histolytica* identifies key components in iron uptake and metabolism. *PLoS One* 9:e107102.
10 Freestone PP, Haigh RD, Williams PH, Lyte M (2003) Involvement of enterobactin in norepinephrine-mediated iron supply from transferrin to enterohaemorrhagic *Escherichia coli*. *FEMS Microbiol Lett* 222:39–43.