Total and Cause-Specific Mortality by Moderately and Markedly Increased Ferritin Concentrations: General Population Study and Metaanalysis

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BACKGROUND: Previous population-based studies of plasma ferritin concentration have not revealed a relationship with total mortality. We tested the possible association of increased ferritin concentrations with increased risk of total and cause-specific mortality in the general population.

METHODS: We examined total and cause-specific mortality according to baseline plasma ferritin concentrations in a Danish population–based study (the Copenhagen City Heart Study) of 8988 individuals, 6364 of whom died (median follow-up 23 years). We also included a meta-analysis of total mortality comprising population-based studies according to ferritin quartiles or tertiles.

RESULTS: Multifactorially adjusted hazard ratios (HRs) for total mortality for individuals with ferritin ≥200 vs <200 μg/L were 1.1 (95% CI 1.1–1.2; P = 0.0008) overall, 1.1 (1.0–1.2; P = 0.02) in men, and 1.2 (1.0–1.3; P = 0.03) in women. Stepwise increasing concentrations of ferritin were associated with a stepwise increased risk of premature death overall (log rank, P = 2 × 10⁻²²), with median survival of 55 years at ferritin concentrations ≥600 μg/L, 72 years at 400–599 μg/L, 76 years at 200–399 μg/L, and 79 years at ferritin <200 μg/L. The corresponding HR for total overall mortality for ferritin ≥600 vs <200 μg/L was 1.5 (1.2–1.8; P = 0.00008). Corresponding adjusted HRs for ferritin ≥600 vs <200 μg/L were 1.6 (1.1–2.3; P = 0.01) for cancer mortality, 2.9 (1.7–5.0; P = 0.00001) for endocrinological mortality, and 1.5 (1.1–2.0; P = 0.01) for cardiovascular mortality. The metaanalysis random effects odds ratio for total mortality for ferritin upper vs reference quartile or tertile was 1.0 (0.9–1.1; P = 0.3) (P heterogeneity = 0.5).

CONCLUSIONS: Moderately to markedly increased ferritin concentrations represent a biological biomarker predictive of early death in a dose-dependent linear manner in the general population.

Increased plasma ferritin concentration is common and the causes are many: increased plasma ferritin >200 and <600 μg/L may be caused by alcohol intake, liver disease, cancer, chronic inflammation, metabolic syndrome, meat intake, and iron supplementation (1), whereas plasma ferritin ≥600 μg/L may be caused by hereditary iron overload (2). Therefore, increased plasma ferritin is considered a biomarker of several diseases or disorders and should be investigated in the individual patient.

In patient studies (3–8), increased plasma ferritin has been shown to be a strong predictor of premature death. Previous population-based studies on risk of premature death by increased plasma ferritin have not found any association, but these studies were either relatively small (9) or used ferritin concentrations in quartiles (10) or tertiles (11), with the highest quartiles or tertiles including a portion of the reference interval for plasma ferritin. Interestingly, a recent study found that probands with hereditary hemochromatosis and ferritin concentrations >1000 μg/L had increased risk of early death (12). This raises the possibility that an increased risk of total mortality in individuals from the general population with increased plasma ferritin may so far have been overlooked, simply because only quartiles or tertiles have been examined.

We used a Danish population–based study comprising 8988 individuals followed for up to 30 years,
during which time 6364 individuals died. As done previously for other biomarker studies of risk of disease or mortality, we tested the hypothesis that moderately (>200 µg/L) and markedly (>600 µg/L) increased plasma ferritin concentrations are associated with increased risk of total and cause-specific mortality in the general population. We first used a categorization model with binary cutoff of ferritin of ≥200 vs <200 µg/L, as well as a dose–response relationship with ferritin <200 µg/L (reference), 200–399 µg/L, 400–599 µg/L, and >600 µg/L. Second, we explored the continuous relationship of increased ferritin concentrations with mortality endpoints. Third, we conducted a meta-analysis of our own study and 2 additional previous population-based studies on risk of increased total mortality according to ferritin concentrations in quartiles or tertiles, indirectly testing the hypothesis that using quartiles or tertiles for risk prediction hides an increased risk because the highest quartiles or tertiles often include part of the reference interval for ferritin concentrations, thereby diluting risk estimates.

Methods

GENERAL POPULATION STUDY
The Copenhagen City Heart Study includes individuals from Copenhagen randomly selected on the basis of the Danish Civil Registration System Code to reflect the adult general population. The participants, age-stratified within 5-year age groups from 20 to 80 years, were examined in 1976–1978, 1981–1983, 1991–1994, and 2003–2004. In 1976–1978, 19 329 individuals were invited and 14 223 participated (74%). In 1981–1983, the previous cohort was invited plus an additional 500 individuals aged 20–24 years; 12 698 participated (70%). In 1991–1994, the previous cohort was invited plus an additional 3000 individuals aged 20–49 years; 10 135 participated (61%). In 2001–2003, the previous cohort was invited plus an additional 2464 individuals aged 20–34 years; 6237 participated (50%). At each examination, participants filled out a questionnaire (e.g., physical activity, smoking, diet, alcohol intake, menopause, and medication use) and attended a health examination including blood samples. Participants were not asked about a previous diagnosis of hemochromatosis.

A total of 8988 participants who had a measurement of plasma ferritin were followed prospectively from the 1981–1983 examination through 2013. The study was approved by a Danish ethics committee and Herlev Hospital, Copenhagen University Hospital. Participants gave written informed consent. The study complied with the Declaration of Helsinki.

MEASUREMENT OF FERRITIN
Plasma samples collected in the 1981–1983 examination were stored at −20 °C until 2009–2010, when we measured ferritin concentrations using EDTA-plasma on an Advia Centaur (Siemens) with a 2-site sandwich immunoassay and direct chemiluminometric technology. Assay precision was tested daily, and assay accuracy was tested monthly by use of an external quality control program. The assay range was 1.0–1650 µg/L. The interassay CV was 4.7% at a ferritin concentration of 46 µg/L, 4.3% at 148 µg/L, and 4.5% at 335 µg/L. The range of plasma ferritin in the population was 1–1524 µg/L.

OTHER CHARACTERISTICS
Individuals were questioned about physical activity, smoking habits, diabetes, alcohol intake, menopause, and medication use. Body mass index was calculated as measured weight in kilograms divided by measured height in meters squared. Plasma total cholesterol was measured enzymatically.

ENDPOINT
By use of the Central Person Registry Number, a number unique to every person living in Denmark, information on total and cause-specific mortality was obtained from time of blood sampling through linkage to the Danish Civil Registration System until April 23, 2013, and to the national Danish Causes of Death Registry until December 31, 2011; owing to the delay in this registry compared with the Danish Civil Registration System, only 6090 of 6364 deaths had information on cause-specific mortality. The national Danish Causes of Death Registry contains information on all underlying and contributing causes of death coded by the Danish National Board of Health on the basis of patients’ death certificates completed by physicians in hospitals, general practice, or forensic medicine. The following International Classification of Diseases (ICD) codes were used to define the causes of death: cancer mortality 140.0–239.9 (ICD-8) and C00–D48 (ICD-10); endocrinological mortality (endocrine, nutritional, and metabolic diseases) 240.0–258.9 (ICD-8) and E00–E90 (ICD-10); and cardiovascular mortality (diseases of the circulatory system) 400.0–448 (ICD-8) and I00–I79 (ICD-10). Median follow-up time for total mortality was 23 years (range 0.03–30 years), during which time 6364 individuals died. No individuals were lost to follow-up.

6 Nonstandard abbreviations: ICD, International Classification of Diseases; HR, hazard ratio.
STATISTICS
We used Stata/SE 13.0 for statistical analysis. Mann–Whitney U tests and Pearson χ² tests were used for continuous and categorical variables. A priori, we stratified main analyses by sex, because disease penetrance associated with iron overload differs markedly between sexes (13).

We mainly analyzed and showed the results using the whole cohort (n = 8988). However, we also performed a sensitivity analysis excluding 767 individuals with ferritin concentrations <20 µg/L, since individuals with very low ferritin concentrations may also have an increased risk of mortality (14) and thus may taint the information of the other observations in the reference group with concentrations <200 µg/L; nonetheless, results were similar to the overall analysis (data not shown).

Cumulative survival was plotted with the use of Kaplan–Meier curves as a function of follow-up in years, and differences between categories of ferritin concentrations were examined by a log-rank test. We used Cox proportional hazards regression to estimate hazard ratios with 95% CIs. The assumption of proportional hazards was tested with the use of Schoenfeld residuals; no violations were observed. Interaction of ferritin concentrations with risk factors on mortality was evaluated by including 2-factor interaction terms, 1 at a time, in the multifactorial Cox regression model. No significant or clinically relevant interactions were observed.

Hazard ratios (HRs) were adjusted for confounders associated with plasma ferritin and/or mortality, i.e., for age and sex or multifactorially for age, sex, leisure time physical activity (almost completely inactive, some activity, regular activity, regular hard physical training), smoking (current vs nonsmoker), diabetes (yes vs no) (not included for analysis of endocrinological mortality), alcohol intake (<7 vs >7 drinks/week), menopause (women only), body mass index (<25 vs ≥25 kg/m²), plasma cholesterol (<5 vs ≥5 mmol/L), antihypertensive medication (yes vs no), diuretics (yes vs no), and medication for heart disease (yes vs no).

Exploring the continuous relationship between plasma ferritin and HR for mortality endpoints, we performed fractional polynomial analyses (15) (fracpoly) in Stata testing 44 different fractional polynomials including a linear model; a linear model for total mortality was not found to be significantly different from the best-fitting fractional polynomial model (deviance difference 4, P = 0.3). Thus, we present the best-fitting linear relationship between continuous plasma ferritin concentration and adjusted HR for total, cancer, endocrinological, and cardiovascular mortality.

As an indicator of premature mortality, we calculated median survival (interquartile range) using the “stsum” command in Stata with age as time-scale. Correction for multiple comparisons in trend tests were done by Bonferroni correction, i.e., with 3 comparisons the P value should be <0.02 (0.05/3) for statistical significance. Population-attributable risk was estimated as \[ f(\text{HR } - 1)/[1 + f(\text{HR } - 1)] \], where f is the frequency of ferritin ≥200 µg/L in the population and HR is the hazard ratio for total mortality.

Finally, for each analysis we calculated the HR that could be detected with 80% power assuming a 2-sided P < 0.05 using NCSS Pass software.

METAANALYSIS
A Priori Search Strategy and Selection Criteria
We decided to include prospective studies published up until December 21, 2013, on the risk of total mortality by ferritin in quartiles or tertiles in general population studies. A search was done on PubMed and through scanning of reference lists of articles identified for relevant studies. The keywords used were “ferritin AND population AND (death OR mortality OR survival OR longevity) NOT (deficiency) NOT (low) NOT (implant) NOT (transplant) NOT (thalassemia).” The search revealed 72 hits. For the metaanalysis, 7 studies were retrieved (6, 9, 10, 16–19); 6 of the 7 studies were excluded due to ferritin not the exposure variable (16), total mortality not the endpoint (17, 18), ferritin not expressed in quartiles or tertiles (9), not a population-based study (6), and not a prospective study (19). Another reference (11) was retrieved from hand search of journals; however, this study did not include total mortality as a primary endpoint, but a stratified vascular and nonvascular mortality (which together may be regarded as total mortality); thus we ended up with 2 studies (10, 11) plus the present study. We used ferritin in tertiles: lowest tertile T1 (range 1–55 µg/L), second tertile T2 (56–126 µg/L), and highest tertile T3 (127–1524 µg/L).

Data Abstraction
The following information was abstracted from each study according to a fixed protocol: authors, year of publication, follow-up in years, country, ethnicity, sex, number of participants, age, endpoint, ferritin interval, risk estimate, and confidence limits.

Statistical Analysis
We combined the summary findings from the 3 studies in a metaanalysis. Statistical analysis was performed with Stata (version 13.0) statistical software, with the Meta command calculating both random and fixed effect measures from reports of effect measures and CIs (20). Statistical heterogeneity was assessed by Q statis-
tic with a corresponding \( P \) value, although lack of power may be an issue with a limited number of studies \((21)\). \( R^2 \) measured the proportion of the observed variance that reflected real difference in effect size rather than sampling error. It was not possible to assess publication bias owing to the low number of studies.

**Results**

**GENERAL POPULATION STUDY**

**Total Mortality**

All potential confounders were associated with mortality and/or plasma ferritin (Table 1). Multifactorially adjusted HRs for total mortality for individuals with ferritin \( \geq 200 \mu g/L \) were 1.1 (95% CI 1.1–1.2; \( P = 0.0008 \)) overall, 1.1 (1.0–1.2; \( P = 0.01 \)) in men, and 1.2 (1.0–1.3; \( P = 0.03 \)) in women (Fig. 1). Stepwise increasing concentrations of ferritin were associated with a stepwise increased risk of premature death overall \((P = 2 \times 10^{-22})\) (Fig. 2) with median survival of 55 years (interquartile range 38–72 years) at ferritin concentrations \( \geq 600 \mu g/L \), 72 years (63–82) at 400–599 \( \mu g/L \), 76 years (67–84) at 200–399 \( \mu g/L \), and 79 years (69–87) at \(< 200 \mu g/L \). (sex-stratified results are shown in Supplemental Table 1, which accompanies the online version of this article at http://www.clinchem.org/content/vol60/issue11). The corresponding HRs are shown in Fig. 1, with the highest risk conferred by ferritin \( \geq 600 \mu g/L \) with a multifactorially adjusted HR overall of 1.5 (1.2–1.8; \( P = 0.0008 \)). Results were similar in men and women separately (Fig. 1) and were still significant after correction for multiple comparisons. Increasing ferritin concentrations were linearly associated with increasing HRs for total mortality \((P = 6 \times 10^{-15})\) (Fig. 3A). The HR for total mortality was 13% (95% CI 9%–14%) higher per 100- \( \mu g/L \) higher plasma ferritin concentration.

On the basis of a frequency of ferritin \( \geq 200 \mu g/L \) of 16% overall, 26% in men, and 6% in women, and on multifactorially adjusted HRs of 1.1, 1.1, and 1.2, respectively, for total mortality, the corresponding population attributable risks for total mortality were 2% overall, 3% in men, and 1% in women.

**Cause-Specific Mortality**

Multifactorially adjusted HRs for individuals with ferritin \( \geq 200 \mu g/L \) were 1.2 (95% CI 1.1–1.3; \( P = 0.005 \)) for cancer mortality, 1.4 (1.1–1.8; \( P = 0.002 \)) for endocrinological mortality, and 1.2 (1.1–1.3; \( P = 0.00006 \)) for cardiovascular mortality (Fig. 4). Correspondingly, stepwise increasing concentrations of ferritin were associated with a stepwise increased cancer mortality \((P = 0.00009)\), endocrinological mortality \((P = 4 \times 10^{-6})\), and cardiovascular mortality \((P = 6 \times 10^{-6})\) (Fig. 4). Multifactorially adjusted HRs for individuals with ferritin \( \geq 600 \mu g/L \) were 1.6 (95% CI 1.1–2.3; \( P = 0.01 \)) for cancer mortality, 2.9 (1.7–5.0; \( P = 0.0001 \)) for endocrinological mortality, and 1.5 (1.1–2.0; \( P = 0.01 \)) for cardiovascular mortality (Fig. 4). Results were still significant after correction.
for multiple comparisons. Increasing ferritin concentrations were linearly associated with increasing HRs for cancer mortality \((P = 0.006)\), endocrinological mortality \((P = 0.006)\), and cardiovascular mortality \((P = 0.01)\) (Fig. 3, B–D). Hazard ratios increased by 10% (6%–13%) for cancer mortality, 15% (4%–25%) for endocrinological mortality, and 10% (3%–22%) for cardiovascular mortality per 100 \(\mu g/L\) higher plasma ferritin. Details of cause-specific mortality for individuals with ferritin \(\geq 200 \mu g/L\) are shown in online Supplemental Table 2, with malignant neoplasms of digestive organs or respiratory tract accounting for 50% of cancer mortality, diabetes accounting for 75% of endocrinological mortality, and ischemic heart disease accounting for 49% of cardiovascular mortality.

On the basis of a frequency of ferritin \(\geq 200 \mu g/L\) of 16% overall, and on multifactorially adjusted HRs of 1.2 for cancer mortality, 1.4 for endocrinological mortality, and 1.2 for cardiovascular mortality, the corresponding population attributable risks were 3% for cancer mortality, 6% for endocrinological mortality, and 3% for cardiovascular mortality.

**METAANALYSIS**

The characteristics of included studies are shown in online Supplemental Table 3. The risk ratio for total mortality for individuals with ferritin in the upper xtile (quartile or tertile) vs reference xtile was 1.0 \([0.9–1.1]; P = 0.3\); \(P\) (heterogeneity, Q-statistic) = 0.5; \(I^2 = 0%\) under the fixed and random effects models (Fig. 5).

**Discussion**

In a Danish population-based study with a median of 23 years of follow-up comprising 8988 individuals and 6364 deaths, we showed that individuals with moderately increased ferritin concentrations at or above a threshold of 200 \(\mu g/L\) have an increased risk of total, cancer, endocrinological, and cardiovascular mortality compared with those with ferritin <200 \(\mu g/L\). Second, we showed a stepwise increased risk of total and cause-specific mortality for stepwise increasing concentrations of ferritin, with the highest risk conferred for ferritin \(\geq 600 \mu g/L\). Third, we showed that increasing concentrations of ferritin were linearly associated with increasing HRs for total, cancer, endocrinological, and cardiovascular mortality.

**Fig. 1. Total mortality by plasma ferritin concentrations.**
cardiovascular mortality. Fourth, we showed in a meta-
alysis that the increased risk of total mortality in in-
dividuals with increased concentrations of ferritin is
concealed when the ferritin concentrations are
expressed in quartiles or tertiles. This study is the largest
and most comprehensive study to date estimating risk
of mortality by moderately and markedly increased fer-
ritin in a general population study.

We calculated median survival age as an indicator
of premature death and demonstrated that markedly
increased ferritin concentrations (ferritin \( \geq 600 \mu g/L \))
are associated with early death. The median survival
age means that 50% have died and 50% are still living at
that age. A subgroup analysis of sex showed that the
overall median survival was primarily driven by the
results in men; however, median survival age is also
dependent on the age at exposure, the length and in-
tensity of the exposure, the age distribution of the pop-
ulation sample, the efficacy of treatment potentially
influencing the biomarker–age relationship, the
promptness of the diagnosis, and the correctness of the
diagnosis (22). Although we were not able to explore
each of these factors in this study, the most important
endpoint of total mortality was 100% promptly and
correctly diagnosed in the Danish registries.

The metaanalysis was based on tabular data from
the literature; thus, the limitation of using this method
may be overlapping categories of ferritin concentra-
tions and different methods of reporting (quartiles and
tertiles; sex-stratified vs not); one study did not even
report the concentration ranges of the ferritin groups
(11). Also, the quartile or tertile ranges determined in a
given study are population-dependent, resulting in differ-
ent concentration ranges from study to study for the fer-
ritin groups. Thus, the combined result from the meta-
alysis may be encumbered with some uncertainty.

Our results are in accordance with previous evi-
dence that increased transferrin saturation is associated
dose-dependently with increased total mortality (23–
25). Another population-based study examined risk of
premature death in individuals of mixed ethnicity with
serum ferritin \( \geq 200 \) vs \( 50–99 \) g/L and did not find
any association (9); however, compared to the present
study, that study was smaller (\( n = 1604 \)), had shorter
follow-up (12 years), and had actual HRs for total mor-
tality of 0.7 (0.4–1.3) and 0.9 (0.4–2.1) in white
women and men, respectively, overlapping with the
present HRs. We calculated that their study (9) had
80% power to detect an increased risk of total mortality
with a HR of 1.7 or more; thus, that study did not have
enough power to detect a modestly increased risk of
total mortality with increased ferritin as observed in
our study. In comparison, our study was well powered
for the analyses, documented by calculation of the
minimal detectable HRs at 80% power. Another study
also found that probands with hereditary hemochro-
matosis and ferritin concentrations \( \geq 1000 \mu g/L \) had
increased risk of early death (12). Finally, iron supple-
mentation has also been associated with risk of prema-
ture death (26).

Fig. 2. Cumulative survival by plasma ferritin concentrations.
The association of increased plasma ferritin with increased risk of cancer and endocrinological mortality is in accordance with previous studies of increased transferrin saturation and cause-specific mortality \((24, 25)\). The association of increased plasma ferritin with increased risk of cardiovascular mortality is in accordance with a previous study of heterozygosity for hereditary hemochromatosis; however, the finding is contradictory to a previous metaanalysis of ferritin concentrations with coronary heart disease, although that metaanalysis did not cover other cardiovascular diseases or mortality \((27)\) and was primarily based on small study populations with shorter follow-up than our study. Thus, in our study, 51% of cardiovascular mortality among individuals with ferritin \(\geq 200 \mu\text{g/L}\) was caused by diseases other than ischemic heart disease, including hypertension \((28)\), cardiomyopathy \((13)\), and electrophysiological changes \((29)\), all diseases of the heart previously associated with iron overload.

A series of considerations are needed to assess the plausibility of associations in epidemiological studies (Bradford–Hill criteria) \((30)\). The association of increased ferritin with total and cause-specific mortality is supported by consistent moderate HRs in a dose–response dependent manner overall and in men and women separately, with low \(P\) values. Our findings on total, cancer, endocrinological, and cardiovascular mortality are consistent with previous studies \((23, 24, 31, 32)\) of iron overload. The effect (death) occurred after measurement of the baseline increased ferritin. Furthermore, the biological mechanism is thought to be generation of oxidative stress as a result of the Fenton reaction \((33)\). Accordingly, the intracellular marker for oxidative stress 8-OxoGuo, a widely used marker of RNA oxidation, is present in patients with hereditary hemochromatosis \((34)\). However, causality may be difficult to claim in this study, since, unlike transferrin saturation, increased ferritin is associated with many diseases other than hereditary iron overload. Taking these factors together, we therefore interpret increased ferritin concentrations as a biological marker of pathogenic processes that reflects severity and presence of a variety of disease states leading to premature death (prognostic marker). Thus, it seems of extreme importance to diagnose and treat the underlying disease.

**Fig. 3.** HRs by increasing ferritin concentration (\(\mu\text{g/L}\)) for total mortality (A), cancer mortality (B), endocrinological mortality (C), and cardiovascular mortality (D).
states in individual patients to potentially improve survival. For ferritin to be a sufficient prognostic biomarker, certain requirements must be met, e.g., low biological and within-day variation and low analytical variation. It has been shown that the within-individual variation for ferritin in men is 5.9%, and the diurnal 24-h oscillating rhythm of ferritin show peaks around a time of 1200 h and the lowest values around 0000 h (35). Furthermore, analytical coefficient of variation is 3.1% (35). Thus, ferritin is a stable marker. The reference interval for ferritin varies between different studies and with the assay used; often the upper reference value for men is 300 µg/L and 200 µg/L for women. These data suggest that for both men and women, the upper reference value should not exceed 200 µg/L. Thus, just as with lipid concentrations (36), a reference interval for ferritin based only on the average adult population, especially in men, may not be suitable and an upper signal cutoff value of ferritin should be based on risk estimates, since risk may be hidden in the upper portion of the conventional reference interval.

Correctness of causes of death is crucial for mortality statistics and health surveillance but also for research purposes. In Denmark, total mortality is based on the Danish Civil Registration System, which updates vital status continuously and is thus considered complete for Danish residents (37). The correctness of the underlying and contributing causes of death relies on the codes and on the physicians who have filled in the death certificates (38). Autopsy rates have in recent years declined in Denmark and are now only 10% (38), a result of a practice of needing consent from the family or the person who died. A metaanalysis on the discrepancy between clinical and autopsy diagnoses estimated that 30% of the diagnoses on death certificates are incorrect (39). Differences in the causes of death may be a result of new diagnostic techniques, increased focus on special diseases, and less focus on ill-defined diseases (38). A Finish validation report estimated that of 7% questionable death certificates, half were reassigned to a different ICD code (40). In Denmark, causes of death are not regularly validated (38). Taken together, our estimates of risk of total mortality likely are very accurate, whereas those for cancer, endocrinological, and cardiovascular mortality have limitations.

In conclusion, moderately and markedly increased ferritin concentrations represent a biological biomarker predictive of early death in a dose-dependent manner.

![Fig. 4. Cause-specific mortality by plasma ferritin concentrations.](image-url)
linear manner in the general population. Increased risk of total mortality in individuals with increased ferritin concentrations is concealed if analyses are performed with ferritin concentrations in quartiles or tertiles.

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