The natural history of serum iron indices for \textit{HFE} C282Y homozygosity associated with hereditary hemochromatosis

SHORT TITLE: Iron indices over time for C282Y homozygotes.

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Abstract (295/250 words)

Background and Aims
There are few longitudinal studies of serum ferritin (SF) and transferrin saturation (TS) levels in individuals homozygous for the C282Y mutation in the haemochromatosis susceptibility gene, HFE. We aimed to characterise the development of elevated iron measures in middle-aged C282Y homozygotes followed for an average of 12 years.

Methods
From 31,192 people aged 40-69 yrs at baseline, we identified 203 C282Y homozygotes (95 males, 108 females), of whom 116 had SF and fasting TS levels measured at baseline (mean age 55 yrs) and 86 were untreated and had iron measures at follow-up (mean 12 yrs). The probabilities of SF at follow-up exceeding clinical thresholds were predicted from baseline SF and TS under a multivariate normal model using all iron measures.

Results
For C282Y homozygotes, at baseline 84% of males and 65% of females had SF above the upper limit of normal, and 37% of males and 3% of females had SF>1000 µg/L. For males with SF 300-1000µg/L at baseline, the predicted probability of progressing to SF>1000 µg/L at follow-up was between 13% and 35%. For females with baseline SF 200-1000 µg/L, the predicted probability was between 16% and 22%. For C282Y homozygotes with normal baseline SF,
<15% were predicted to develop SF >1000 µg/L if left untreated. For male C282Y homozygotes, higher TS predicted elevated SF at follow-up.

**Conclusion**

The majority of C282Y homozygotes who are likely to develop SF levels sufficient to place them at risk of iron overload-related disease will have done so by age 55 years. Elevated TS > 95% at age 55 years in males increases the likelihood that SF levels will be elevated at age 65 years but this effect is absent in females, most likely due to the influence that menopause has on iron loading in women.
Introduction

While 60-80% of people who are homozygous for the most common HFE mutation (C282Y) associated with hereditary hemochromatosis (HH)¹ develop abnormal iron indices, it is currently difficult to predict who will develop elevated iron stores and be at subsequent risk of iron overload-related disease. C282Y homozygotes are best considered to be genetically at-risk of progressing along a spectrum of disease broadly categorised as: 1) no abnormality; 2) iron overload without symptoms; and 3) iron overload with signs and symptoms of HH such as cirrhosis, liver fibrosis and arthritis (defined as iron overload-related disease). We have recently shown, using objective criteria, that 28% of male and 1% of female C282Y homozygotes develop iron overload-related disease by, on average, age 65 yrs².

Serum ferritin (SF) levels are correlated with body iron stores³-⁵ and, when elevated to greater than 1000 µg/L, are associated with an increased risk of cirrhosis of the liver and clinical symptoms of haemochromatosis²,⁶-¹¹. Clinical guidelines reflecting these findings have been developed recommending that percutaneous liver biopsy and subsequent therapeutic venesections should be offered to all C282Y homozygotes with SF>1000 µg/L¹²-¹⁴. Conversely, C282Y homozygotes with normal SF levels (SF<200 µg/L for pre-menopausal females and SF<300 µg/L for males and post-menopausal females) do not require further assessment of iron overload or therapeutic venesection, although many
clinicians recommend voluntary blood donation as a prophylactic measure for which there is evidence of good compliance\textsuperscript{15}.

Despite these clinical recommendations for C282Y homozygotes with SF\textgreater{}1000 µg/L, there is little evidence to guide the clinical follow-up and management of C282Y homozygotes with SF levels < 1000 µg/L. This is because it is not known what proportion of C282Y homozygotes with SF < 1000 µg/L progress to SF\textgreater{}1000 µg/L later over different age and time intervals. The only two previous longitudinal studies of the history of SF levels for untreated C282Y homozygotes with at least 10 years follow-up were carried out on a combined total of 33 people studied for 17 or 23 years\textsuperscript{16,17}. Neither was able to provide meaningful predictive information about the likelihood of progression to SF\textgreater{}1000 µg/L for C282Y homozygotes over time, although it appeared that SF levels did not rise uniformly for all C282Y homozygotes.

To clarify this issue we genotyped participants, aged 40-69 yrs at baseline in a prospective cohort study, for the C282Y mutation in the \textit{HFE} gene, and measured SF and transferrin saturation (TS) levels from blood samples taken at baseline and again 10-15 years later. Statistical models were developed to predict the probability that future SF levels would exceed clinically relevant thresholds given baseline SF and/or TS measures.
Study Methods

The present study, known as HealthIron, is a sub-study of the Melbourne Collaborative Cohort Study (MCCS\textsuperscript{18}). Between 1990 and 1994, 41,528 people (24,479 females) in the target age range 40-69 years were enrolled in the MCCS. Participants were recruited via the electoral roll (voting is compulsory in Australia), advertisements and community announcements in local media. All participants gave a blood sample at baseline. For most participants, blood spots were aliquotted onto Guthrie cards; for the remaining participants, buffy coats were extracted and stored in liquid nitrogen. Plasma was also retained, transported at 4°C and stored frozen in liquid nitrogen.

For the HealthIron study, eligibility was restricted to the 31,192 people born in Australia, the United Kingdom, Ireland or New Zealand (\textit{i.e.} almost exclusively of northern European ancestry). Subjects born in southern Europe (Italy, Greece or Malta) were excluded due to the lower prevalence of the \textit{HFE C282Y} mutation in southern Europe compared to northern Europe. Genotyping was undertaken from 2003 using baseline samples for all eligible participants who had not withdrawn from the MCCS. DNA was extracted from Guthrie cards (n=23,484) using Chelex reagent or from buffy coats (Corbett Buffy Coat CorProtocol\textsuperscript{TM} 14102) (n=7708) and genotyped for the nucleotide changes that correspond to the amino acid substitutions C282Y and H63D in the HFE protein using Applied Biosystem Taqman real-time PCR probes as previously described\textsuperscript{2}. 
A comprehensive active follow-up of MCCS participants began in 2003 and was completed in June 2007. Letters of invitation to participate in the HealthIron study were sent to a sample of 1,438 participants that included all C282Y homozygotes and a stratified random sample of participants from other HFE genotype groups. Participants who attended a study centre completed a computer-assisted personal interview (which included questions on iron-related conditions, treatment and blood removal) and provided a cheekbrush DNA sample for confirmatory HFE genotyping (Applied Biosystem 7000 real-time PCR with Taqman probes). Blood samples were collected for measurement of iron indices and liver enzymes using Roche automated assays, and were paired for analysis with their stored baseline plasma samples. Although baseline measurements were made from plasma, the abbreviation SF is used here. At follow-up, fasting blood samples were collected in the morning, while at baseline, 67% of all MCCS participants were fasting. Those C282Y homozygotes diagnosed by family physicians between baseline recruitment and follow-up received standard medical care by their treating physicians, which included therapeutic phlebotomy when clinically indicated.

All subjects gave written, informed consent to participate in both MCCS and the HealthIron sub-study. Both study protocols were approved by The Cancer Council Victoria's Human Research Ethics Committee.
**Statistical Methods**

We defined elevated SF level as > 300 µg/L for males and post-menopausal females and > 200 µg/L for pre-menopausal females. SF was also compared with a second threshold of 1000 µg/L since this is associated with an increased risk of iron overload-related disease, including asymptomatic cirrhosis. TS was considered to be elevated when > 50% for males and > 45% for females. For analysis, C282Y homozygotes were classified separately on the basis of their venesection status (never, before baseline, or after baseline but before follow-up) and their blood donation history (never, former (ceased before baseline), or current (still donating at baseline)).

The prevalence of an iron measure exceeding a clinically relevant threshold was estimated as the observed proportion and presented with 95% confidence intervals. For all statistical analyses of the continuously distributed SF levels the values were (natural) log transformed. Comparisons of mean SF and TS measurements between groups were made using t-tests with two-sided p-values.

An important aspect of clinical management of C282Y homozygotes is predicting whether their SF is likely to reach a level of clinical concern. Therefore, we developed models to predict the probability that SF levels at follow-up reach three specified thresholds (300, 500 and 1000 µg/L) given the baseline values of SF and TS. Separate models were fitted for men, pre-
menopausal women and post-menopausal women because of previously published evidence (Koziol et al. (2001), Whitfield et al. (2003)) that the distribution of iron indices differs in these three groups. For C282Y homozygotes diagnosed and treated by venesection during the period of the study, we included only their baseline SF and TS measurements (i.e. pre-venesection results) in the statistical analyses.

We assumed that baseline SF, baseline TS and follow-up SF jointly followed a multivariate normal distribution. Under this assumption, the conditional distribution of SF at follow-up is univariate normal (i.e. for specified values of the other variables, the follow-up SF has a univariate normal distribution). For each baseline SF & TS combination, the predicted probability that follow-up SF exceeds any of the three clinical thresholds (300, 500 and 1000 μg/L) was obtained by reference to the cumulative normal distribution. From these models, we also estimated the relative changes in mean SF from baseline to follow-up. For computational ease, we used the WinBUGS software (Spiegelhalter et al. (2003)) for the statistical analysis, since the predicted probabilities are generated directly as part of the model fitting process. WinBUGS is generally used for Bayesian analyses, but because we used noninformative prior distributions, our results are essentially identical to those obtained from standard maximum likelihood techniques for estimating the parameters and their confidence intervals.
Results

Features of C282Y homozygotes

A total of 203 C282Y homozygotes (95 males, 108 females) were identified in this cohort of 31,192 people of northern European extraction. Of these, 146 (72%) participated in the follow-up and 143 provided blood samples that yielded at least one SF or TS measurement at baseline or follow-up (Table 1). The average time between the baseline and follow-up visits was 12.0 years (range 9.8 – 14.3 yrs).

The average age of C282Y homozygotes at baseline was 53.5 years (s.d. 8.9) for males and 54.9 years (s.d. 8.4) for females, with more than half aged between 45 and 60 years of age. For females with known menopausal status, 43 of 69 (62%) were post-menopausal at baseline. At baseline, 94 (64.4%) were fasting and 120 (82.2%) were fasting at follow-up.

Serum ferritin and transferrin saturation at baseline

When assessing iron indices at baseline, those C282Y homozygotes who had been diagnosed and venesected before baseline (1 female and 5 males) were excluded.

Table 1 shows the venesection status and blood donation history of the cohort at baseline. Men diagnosed with iron overload and treated before the follow-up visit (n = 25) had higher baseline SF on average than those who had not been
diagnosed before the follow-up visit (n = 26) (927 µg/L v 521 µg/L) although the p-value was large (p = 0.12). There were too few women diagnosed and venedected after baseline with both baseline SF and menopausal status known (2 pre-menopausal and 7 post-menopausal) to make a valid comparison between groups.

For pre-menopausal women, there was an association between baseline SF and recent blood donation, with SF levels in current donors greater that those in participants who had never donated by 8.80 fold (95% CI (2.07, 37.35), p=0.006); SF levels in former donors were similar to those in the never donated group (p = 0.55).

For men and post-menopausal women, there was no strong evidence of associations between blood donation and baseline SF. For never donated versus former donor and never donated versus current donor, the p-values were 0.11 and 0.70 for men, and 0.075 and 0.34 for post-menopausal women respectively.

The proportion of TS and SF measurements exceeding clinically relevant thresholds is displayed in Figure 1. Seventy eight percent of men (95% CI (64%, 88%)) and 52% of women (95% CI (40%, 65%)) had both indices elevated at baseline. More than one third of men (19/51 = 37%, 95% CI (24%, 52%)) but only 3% of women (95% CI (0.5%, 12%) had a SF > 1000 µg/L at baseline. All individuals with SF>1000 µg/L had elevated TS.
**Change in serum ferritin between baseline and follow-up**

There was substantial variation between individuals in the change of SF from baseline to follow-up (Figure 2). Of the 24 men who had never been venedected and who had baseline and follow-up SF measures, 14 had follow-up SF greater than the corresponding baseline value, and the other 10 had a value lower than baseline. Of the 48 women who had never been venedected and who had baseline and follow-up SF measures, 14 (8 post-menopausal, 4 pre-menopausal and 2 unknown) had a follow-up SF value that was lower than the corresponding baseline value. SF increased from baseline to follow-up in 17 (81%) of 21 pre-menopausal women and 15 (65%) of 23 post-menopausal women.

The statistical modelling showed that for women, baseline TS was only weakly correlated with follow-up SF ($r = 0.10$, 95% CI -0.15 to 0.61 for pre-menopausal women and $r = 0.27$, 95% CI -0.10 to 0.58 for post-menopausal women). Thus, the models for women were re-fitted using baseline and follow-up SF and assuming a bivariate normal distribution. Table 2 shows the results from the final models. For men, the mean SF increased by only 11% during follow-up (95% CI -14% to 43%), $p=0.38$). For pre-menopausal women, the mean SF increased 3.70 fold (95% CI (1.70, 8.40), $p=0.0015$) and for post-menopausal women, 1.31 fold (95% CI (0.77, 2.22), $p=0.31$).
Predicted probabilities that follow-up SF values would exceed 300, 500 or 1000 µg/L are shown in Figure 3 separately for pre- and post-menopausal women, and for men using three values of baseline TS.

For men, the predicted probability of follow-up SF exceeding 1000 µg/L had a strong positive association with baseline SF. For men with baseline SF of 1000 µg/L, the predicted probability that follow-up SF exceeded 1000 µg/L ranged from 29% (for a baseline TS of 55%) to 56% (for a baseline TS of 95%), in all cases more than 20 times larger than the corresponding probability for a baseline SF of 100 µg/L (which was less than 2% for all baseline values of TS). Men with the observed average baseline values of TS and SF of 75% and 600µg/L, respectively, had a predicted probability of follow-up SF exceeding 1000 µg/L of 25%. This prediction accords well with the observed prevalence of SF > 1000 µg/L at follow-up among untreated male C282Y homozygotes of 31%, given the large prevalence of elevated SF at baseline among male C282Y homozygotes. By comparison, the predicted probability of SF > 1000 µg/L at follow-up was only twice as great for those women with baseline SF of 1000 µg/L compared to those women with baseline SF of 100 µg/L (18% v 9% for pre-menopausal women and 26% v 13% for post-menopausal women).
Discussion

We have studied the natural history of serum ferritin and transferrin saturation measurements over a mean period of 12 years in a sample of C282Y homozygotes who were participating in a large prospective cohort study. The majority of male C282Y homozygotes (84%) had elevated SF values at baseline (mean age 55 years) and more than one third had SF > 1000 µg/L, suggesting that significant iron loading had developed in a substantial proportion of male C282Y homozygotes by this age. A similar high prevalence was observed at follow-up for non-treated male C282Y homozygotes, although the increase in average SF for this period was only 11%. By comparison only 3% and 7% of women had SF > 1000 µg/L at baseline and follow-up respectively.

The predictive statistical models showed that male C282Y homozygotes with baseline SF values between 300 µg/L and 1000 µg/L at baseline had a 25% chance of progressing to SF > 1000 µg/L an average of 12 years later. Eighteen percent of female C282Y homozygotes progressed from SF values between 200µg/L and 1000 µg/L to SF > 1000 µg/L during the same time period. These data, coupled with the high prevalence of elevated baseline SF for both sexes, indicate that there are a substantial number of at-risk individuals who require ongoing monitoring for iron overload even after the age of 55 years. However, of those individuals who had a normal SF at age 55 years, less than 15% of untreated men and women developed SF > 1000 µg/L over a 10-15 year period. We provide evidence that transferrin saturation reflects the underlying
pathological process of excess iron accumulation since male C282Y homozygotes in whom baseline fasting TS was greater than 95% were more likely to have a follow-up SF exceeding 1000 µg/L.

We have previously shown that male C282Y homozygotes with SF > 1000 µg/L are at risk of iron overload-related disease (Allen et al. (2008)) and should therefore be treated with therapeutic phlebotomy. Our current study shows that male C282Y homozygotes with SF < 1000 µg/L but SF > 300 µg/L who have TS > 95% have as much as a one third chance of progression to SF > 1000 µg/L and therefore should also be treated. In contrast, the probability of SF progressing to levels greater than 1000 µg/L between a mean age of 55 and 65 years is low for all female C282Y homozygotes and for those male C282Y homozygotes with SF < 1000 µg/L and TS < 95%. Since it is not yet known what the risk of disease is for C282Y homozygotes with elevated SF that is less than 1000 µg/L, and that for some of these individuals there is a reasonable chance they will progress to SF > 1000 µg/L, consideration should be given to prophylactic therapeutic phlebotomy for these C282Y homozygotes as well.

Our results confirm and extend data reported by earlier studies. The prevalence of elevated SF and TS, and of SF > 1000 µg/L, at baseline in our study are similar to those reported in other cross-sectional studies 2, 20-25. The only two previous longitudinal studies of SF levels from untreated C282Y homozygotes followed for more than a decade were based on a combined total of 33 individuals studied for 17 or 23 years 16, 17. In the Copenhagen City Heart
Study there were 23 C282Y homozygotes, and the mean SF and TS measures increased slightly in these individuals (over a follow-up period of up to 25 years) irrespective of age. In 10 C282Y homozygous participants (6 females, 4 males) in the Busselton Study in Western Australia, SF levels increased in 4, remained stable in 4 and decreased in 2 over a 17 year period. The median age of these participants at baseline in 1981 was 30 years, considerably younger than participants in the HealthIron study whose median age at baseline was 54 years. The increase in median SF levels reported in C282Y homozygotes from the Busselton Study, from 271 µg/L to 593 µg/L, is similar to the trends observed in our study. Waalen et al. (2008) suggest that SF levels in most C282Y homozygotes will reach a plateau with no further increase. In addition, Yamashita and Adams (2003) showed that of 22 C282Y homozygotes (18 women, 4 men) with initially normal SF levels followed for a median of 4 years, 20 (91%) failed to show any appreciable increase in SF level.

These findings are consistent with both human and animal studies, which suggest that a plateau in iron loading is reached over time. For example, McLaren et al. (1991) showed that iron absorption declines in hemochromatosis patients as their iron load increases, suggesting that iron accumulation is physiologically self-limiting.

Our analysis reveals substantial sex differences in the prevalence of elevated SF and increase in SF levels in C282Y homozygotes. Women had a much lower prevalence of elevated SF at baseline, but showed a greater although not
significant increase in SF from baseline to follow-up than men, the majority of
whom, if untreated, had constantly elevated SF. There were few women with SF
values > 1000 µg/L at either baseline or follow-up, and we have shown
previously that the prevalence of disease symptoms in female C282Y
homozygotes is low. It is interesting to note that there was an increase in SF
from baseline to follow-up in women which included the time during which the
majority underwent menopause, suggesting that menopause influences the
development of elevated SF in women. It is conceivable that the peak time of
iron accumulation in female C282Y homozygotes might not have been reached
by the conclusion of the study. The predicted probability of SF exceeding 1000
µg/L at follow-up was much more sensitive to the value of baseline SF in men
than women, although these predictive probabilities are higher for men with
elevated SF than women. The fact that elevated TS has an effect on the
development of elevated SF in men but not women is possibly due to the effect
of menopause.

Our cohort constitutes the largest number of C282Y homozygotes studied
longitudinally over a 10-15 year period, and the follow-up was completed at an
age when iron loading would be expected to have occurred. Although we either
investigated explicitly or accommodated implicitly through exclusion criteria the
influence on TS and SF of blood donation, diagnosis, treatment and
menopausal status, we did not screen for Coeliac disease or perform
endoscopies on all participants so there may be other unspecified reasons for
blood loss. Results from one study suggest that regular blood donation (as
opposed to therapeutic venesection) does not decrease the severity of iron overload\textsuperscript{27}, which is consistent with our data.

One potential limitation of our study is that we could not use follow-up iron studies on treated C282Y homozygotes because therapeutic venesection had interrupted the natural course of disease in these individuals. Since the majority of those treated had evidence of iron overload-related disease at diagnosis\textsuperscript{2} there is the possibility that there are two groups of C282Y homozygotes – those with a rapidly rising trajectory and those with iron levels that do not necessarily continue to increase later in life. The role of other dietary and genetic influences on TS and SF are the subject of on-going study in the MCCS and may be helpful in delineating whether there are in fact different influences at play in development of both iron accumulation and iron overload-related disease.

In conclusion, the majority of C282Y homozygotes who are likely to develop SF levels sufficient to place them at risk of iron overload-related disease will have done so by the age of 55 years. The risk of developing SF > 1000 µg/L and therefore iron overload-related disease is higher in those with elevated SF and TS at age 55 compared to those with normal iron indices at the same age.
Table 1: Venesection and blood donation status at baseline for C282Y homozygotes relative to sex and, for females, menopausal status.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Venesection status</th>
<th>Total</th>
<th>Blood donation at baseline</th>
<th>Total</th>
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<tr>
<td></td>
<td>never after baseline</td>
<td></td>
<td>never former current</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>34# 27@</td>
<td>61^</td>
<td>29 20 12</td>
<td>61</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre-menopausal</td>
<td>23 3</td>
<td>26</td>
<td>13 6 7</td>
<td>26</td>
</tr>
<tr>
<td>post-menopausal</td>
<td>31 11</td>
<td>42</td>
<td>23 16 3</td>
<td>42</td>
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<tr>
<td>unknown menopausal status</td>
<td>4 4</td>
<td>8 6 1 1</td>
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<tr>
<td></td>
<td>58% 18$</td>
<td>76%^</td>
<td>42 23 11</td>
<td>76</td>
</tr>
</tbody>
</table>

# Both baseline and follow-up SF measures were available for 24, 2 had baseline but no follow-up and 8 had follow-up measures but no baseline.

$ Baseline SF measures were available for 13.

% Both baseline and follow-up SF measures were available for 48, 4 had baseline but no follow-up and 6 had follow-up measures but no baseline.

^ 5 males and 1 female were excluded due to diagnosis and treatment pre-baseline.

& 19 females had hysterectomies before baseline; 1 was pre-menopausal, 10 were post-menopausal and 8 had unknown menopausal status.
**Table 2**: Estimates from the multivariate normal model for baseline TS, baseline SF and follow-up SF.

(a) Male C282Y homozygotes

<table>
<thead>
<tr>
<th>Means</th>
<th>Estimate</th>
<th>95% Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geometric Mean baseline SF</td>
<td>625 µg/L</td>
<td>444 to 864 µg/L</td>
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<tr>
<td>Geometric Mean follow-up SF</td>
<td>698 µg/L</td>
<td>509 to 952 µg/L</td>
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<tr>
<td>Geometric Mean baseline TS</td>
<td>72%</td>
<td>66% to 77%</td>
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<tr>
<td>Ratio of follow-up geometric mean SF to baseline geometric mean SF</td>
<td>1.11</td>
<td>0.87 to 1.43</td>
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**Correlations**

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<th>95% Confidence Limits</th>
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</thead>
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<tr>
<td>Baseline TS &amp; Baseline SF</td>
<td>0.78</td>
<td>0.65 to 0.87</td>
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<tr>
<td>Baseline SF &amp; Follow-up SF</td>
<td>0.86</td>
<td>0.75 to 0.93</td>
</tr>
<tr>
<td>Baseline TS &amp; Follow-up SF</td>
<td>0.74</td>
<td>0.54 to 0.86</td>
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(b) Female C282Y homozygote pre-menopausal at baseline

<table>
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<tr>
<th>Means</th>
<th>Estimate</th>
<th>95% Confidence Limits</th>
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</thead>
<tbody>
<tr>
<td>Geometric Mean baseline SF</td>
<td>54 µg/L</td>
<td>25 to 114 µg/L</td>
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<tr>
<td>Geometric Mean follow-up SF</td>
<td>199 µg/L</td>
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<td>Ratio of follow-up geometric mean SF to baseline geometric mean SF</td>
<td>3.70</td>
<td>1.70 to 8.40</td>
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<tr>
<td><strong>Correlations</strong></td>
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<tr>
<td>Baseline SF &amp; Follow-up SF</td>
<td>0.27</td>
<td>-0.15 to 0.61</td>
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(c) Female C282Y homozygote post-menopausal at baseline

<table>
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<tr>
<th>Means</th>
<th>Estimate</th>
<th>95% Confidence Limits</th>
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<tr>
<td>Geometric Mean baseline SF</td>
<td>305 µg/L</td>
<td>197 to 467 µg/L</td>
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<tr>
<td>Geometric Mean follow-up SF</td>
<td>400 µg/L</td>
<td>271 to 593 µg/L</td>
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<tr>
<td>Ratio of follow-up geometric mean SF to baseline geometric mean SF</td>
<td>1.31</td>
<td>0.77 to 2.22</td>
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<td><strong>Correlations</strong></td>
<td></td>
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<tr>
<td>Baseline SF &amp; Follow-up SF</td>
<td>0.27</td>
<td>-0.10 to 0.58</td>
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References


