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Health Utilities Associated with Hemoglobin Levels and Blood Loss in Postmenopausal Women: The Women's Health Initiative

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ABSTRACT

Objectives: The purpose of our study was to use health-related quality of life data from the Women's Health Initiative to calculate health-related utility weights and examine differences in these health utility weights across different hemoglobin (Hgb) levels. These utility weights could then be used in future cost-effectiveness studies. **Methods:** Health utility weights were measured by the Short Form-6D (SF-6D), a health utility index derived from the Short Form Medical Outcomes questionnaire. Adjusted least square means were calculated for each level of Hgb at baseline and in longitudinal regression analysis the relationship between change in Hgb and change in the SF-6D was examined. Both baseline and longitudinal analyses were performed for all postmenopausal women and separately for those with self-reported heart failure, cancer, and osteoarthritis. **Results:** Women with Hgb in the anemic range had lower health utility weights than those with higher Hgb levels. Longitudinally, a loss of of 2 g/dl Hgb or more was associated with a statistically significant and clinically meaningfully decline in SF-6D in all participants and also in the group of participants with cancer and osteoarthritis, but not in those with heart failure. **Conclusions:** Lower levels of Hgb and a loss of Hgb are associated with a statistically significant and clinically meaningful decrement in health utility in all postmenopausal women we studied and also in those with chronic conditions.

Keywords: health utilities, hgb, osteoarthritis, postmenopausal.

Introduction

The economic impact of blood loss leading to anemia can be considerable. A recent study examined the cost differences between patients with and without anemia in six different chronic diseases: heart failure (HF), rheumatoid arthritis, inflammatory bowel disease, chronic obstructive pulmonary disease, chronic kidney disease, and cancer [1]. After adjusting for comorbiditiy and disease severity they found patients with anemia incurred excess annual costs that ranged from $7000 in rheumatoid arthritis to $29,000 in patients with congestive HF.

Anemia occurs when a person's blood does not have enough hemoglobin (Hgb). Hgb is a protein in red blood cells that carries oxygen from lungs to the rest of the body. The World Health Organization has classified for women a Hgb level less than 12 g/dl as anemia [2]. A decrease in Hgb more than 2 g/dl from baseline has been considered to be clinically important blood loss [3]. Among women with a Hgb level lower than 14 g/dl at baseline, the 2 g/dl Hgb decrease would have resulted in the World Health Organization-defined anemia. For women who are anemic at baseline, the 2 g/dl Hgb decrease would have led to even more serious anemia.

Hgb levels reflect a steady state between both the rate of production of red blood cells, rate of destruction, and chronic blood loss. Although certain chronic diseases are known to be associated with perturbations in this dynamic process, in some cases the treatment of these chronic diseases leads to alterations in Hgb levels. For example, nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for osteoarthritis and have been associated with gastrointestinal toxicity-associated blood loss [4].

Blood loss has both economic and quality of life (QoL) implications. Therefore when considering the trade-offs between the benefits of medical therapy versus its negative side effects for a specific disease, understanding the effects of these therapies on Hgb levels and its attendant effects on both the costs and QoL is important. Indeed, health techonology assessment groups and reimbursement authorities consider the cost per quality-adjusted life years when making reimbursement decisions for drugs and medical devices.

Recent work on the measurement of health utility for anemia-related health states has been limited to patients with anemia associated with cancer treatment [5], treatment for hepatitis C [6,7] or renal failure [8]. The Center for the Evaluation of Value and Risk in Health, at Tufts University's Cost-Effectiveness Analysis Registry has included utility weights for different Hgb levels from eight studies [6–13]. None of these studies has looked at QoL or utility weights related to Hgb levels in a healthy population. The assignment of utility weights to Hgb levels in a larger population can provide an excellent source for future studies of the cost-effectiveness of interventions developed to mitigate blood loss and perhaps prevent anemia.

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The purpose of our study was to use health-related QoL data from the Women's Health Initiative (WHI) to calculate health utility weights and examine differences in these health utility weights across different Hgb levels. Given the lack of information on how clinically important blood loss affects patients' QoL, our study also assessed the relationship between the loss in Hgb and the change in health utility. The WHI study includes a large cohort of postmenopausal women that has high quality data on the Short Form Medical Outcomes questionnaire (SF-36), as well as recordings of Hgb levels. These data are an ideal source to address the questions:

- What are the utility weights for varying levels of Hgb adjusted for confounding factors in postmenopausal women? That is, do women with anemia have lower health utilities?
- What is the relationship between the loss in Hgb and the change in health utility over time? That is, do women who lose 2 g Hgb or more over 3 years have worse health utilities compared to women whose Hgb level did not drop?

Methods

Study population

The WHI is a national study that recruited women through 40 US clinical sites during 1993–1998 [14,15]. Study participants were women aged 50 to 79 years at baseline. Women were excluded if they did not plan to reside in the area of the study clinic for at least 3 years, had medical conditions predictive of less than 3 years of survival, or had complicating conditions such as alcoholism, mental illness, or dementia. Those eligible for either the clincal trial or observational arms completed baseline assessments, including a complete blood count, clinical exam, medication inventory, questionnaires including self-reported diseases and SF-36 questionnaires. A standardized written protocol, centralized training of local clinical staff, local quality control, and periodic quality assurance visits by the clinical coordinating center were used to maintain uniform data collection procedures at all study sites. Reproducibility of WHI questionaire data was evaluated in a random subsample at 10 weeks with good to excellent reproducibility (weighted κ 0.77 to 0.99) [14].

For the longitudinal analysis, participants in the observational study or those in the control arms of the randomized trials were considered as the basis for the follow-up sample. In addition, the eligible participants needed to complete the 3-year follow-up visit questionnaires and provide a blood sample for analysis. Women in the treatment arms of the randomized trials were excluded from the follow-up analysis due to concern for potential influence on treatment on Hgb level and/or ultility weights at the 3-year follow-up assessment.

Measures

Hemoglobin levels

A complete blood count was drawn and analyzed by certified laboratories at each of the 40 clinical sites. Baseline Hgb levels and change in Hgb levels over a 3-year period were obtained.

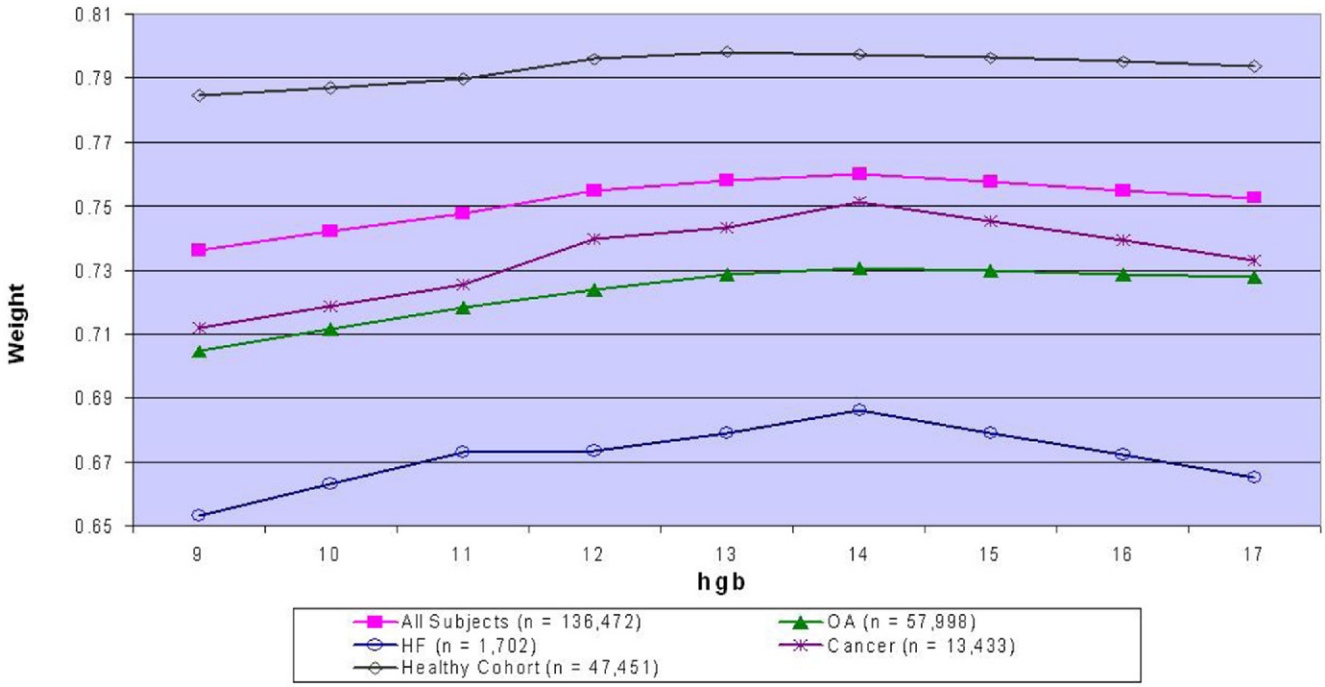

Fig. 1 – Adjusted* baseline Short Form-6D utility weights by hemoglobin (Hgb) level in postmenopausal women participants in the Women's Health Initiative study. *Data for all subjects was adjusted for baseline Hgb group, age, race/ethnicity, education level, body mass index, exercise level, depression, randomized controlled trial status, and self-reported history of disability, bleeding problems, intestine removal, any overnight hospitalizations in prior 2 y, liver disease, diabetes, lupus (not on treatment), stroke or heart attack, rheumatoid arthritis (not on treatment), cancer, heart failure, and osteoarthritis. In patients with osteoarthritis (OA) adjusted variables were the same as those for all subjects, except excluding osteoarthritis. In patients with heart failure (HF) adjusted variables were the same as those for all subjects, except excluding HF. In patients with cancer adjusted variables were the same as those for all subjects, except excluding cancer. For patients int the healthy cohort adjusted variables were the same as those for all subjects, exept excluding liver disease, diabetes, lupus (not on treatment), stroke or heart attack, rheumatoid arthritis (not on treatment), cancer, heart failure, and osteoarthritis.

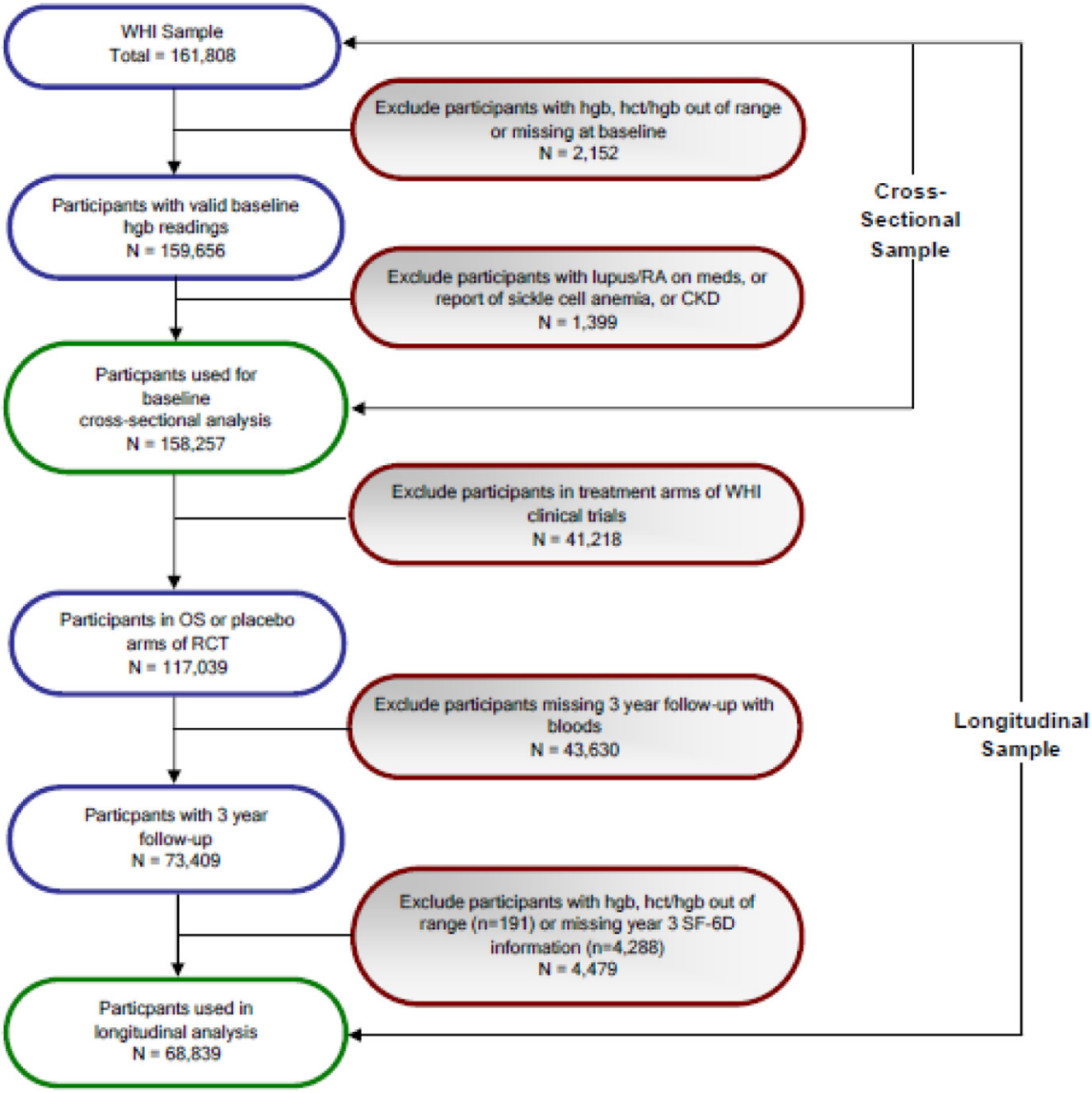

Fig. 2 – Women's Health Initiative (WHI) study sample selection diagram. RA, rheumatoid arthritis; CKD, chronic kidney disease; OS, osteoarthritis; RCT, randomized controlled trial.

SF-36 and Short Form-6D (SF-6D) utility measurement

The SF-6D is a health utility index derived from the SF-36 health-related QoL. The SF-6D has six dimensions: physical functioning, role limitations, social functioning, pain, mental health, and vitality. Each dimension has between two and six levels. More than 18,000 health states have been classified using the SF-6D [16]. The SF-6D algorithm estimates a preference-based measure of health from the responses obtained in the SF-36. SF-6D values range between zero (indicating death) and one (indicating excellent health). The SF-6D preference weights were derived from a sample of the general population using the valuation technique of standard gamble. The advantage of using the SF-6D rather than using the SF-36 is that the SF-6D weights allow for calculation of quality-adjusted life years that can be used to compare the relative merits (cost-effectiveness) of different types of interventions. A difference of 0.025 in the SF-6D has been judged to be a the minimal clinically important difference (MICD) in QoL for this index [17].

Covariates

Sociodemographic factors (age, race/ethnicity, and education) were asked at baseline. Disability status was based on a response to current job status as "disabled, unable to work." Physical activity was quantified as a continous variable in metabolic equivalents per week using a validated questionaire and published database of physical activity and metabolic equivalent intensities. Baseline depressive symptoms were assessed by self-report using Burnam's eight-item scale for depressive disorders (major depression and dysthymia) [18,19]. The distribution of scores was highly skewed, suggesting a binomial distribution. There-

fore, as has been done in other studies, a cutpoint of 0.06 of higher was used to dichotomize the continuous score.

Several comorbidities were assessed:

- The presence of cardiovascular disease was based on an affirmative answer to one of the following questions: "Did a doctor ever say that you had a stroke?" or, "Did a doctor every say that you had a heart attack?"
- The identification of liver disease was based on an affirmative answer to the following question: "Did a doctor ever say that you had any of the following health problems? Liver disease (chronic active hepatitis, cirrhosis, or yellow jaundice)?"
- Women with diabetes were identified based on the question, "Did a doctor ever say that you had diabetes or high blood sugar when you were not pregnant?"
- Gastrointestinal surgery history was determined based on an affirmative answer to the following question: "Has a doctor told you that you have any of the following conditions or have you had any of the following procedures . . . Part of intestines taken out."
- Women were identified as having osteoarthritis, HF, or cancer based on the following questions: osteoarthritis was identified by an affirmative response to the question, "Did your doctor ever say that you had arthritis?" coupled with any response other than "rheumatoid arthritis" to the follow-up question, "What type of arthritis do you have?"

* The presence of HF was determined by an affirmative response to the question, "Did a doctor ever say that you had any of the following health problems? Heart failure?" or an affirmative response to: "Has a doctor ever told you that you had heart problems, problems with your blood circulation, or blood clots?" coupled with the selection of "Heart failure or congestive heart failure" to the follow-up question, "Please mark the conditions or procedures below that a doctor said you had."

* The identification of participants with cancer included an affirmative response to any of the following questions: "Did a doctor ever say you had breast cancer?", "Did a doctor ever say you had colon, rectum, bowel, or intestinal cancer?", "Did a doctor ever say you had endometrial cancer (cancer of the lining of the uterus or womb)?", "Did a doctor ever say you had skin cancer?" (not melanoma), "In the last 10 years, did a doctor ever say that you had any other cancers?", and "Did a doctor ever say that you had cancer, a malignant growth, or tumor? (This does not include fibroids of the uterus.)" coupled with, "What kind of cancer did you have?"

- Overnight hospitalization was determined based on an affirmative answer to the following question: "Have you been hospitalized overnight at any time during the past 2 years?" Body mass index was calculated and respondents were divided into categories based on their response (<25, 25–29.9, 30–34.9, 35–39.9, and ≥40).

Statistical analyses

For the cross-sectional analyses using baseline data, demographic characteristics and baseline service use are presented. Because the relationship at baseline between Hgb and SF-6D was not linear, three cutpoints were chosen where the relationship appeared to be linear (<12, 12–13.9, ≥14 g/dl) (Fig. 1). A test of linear contrasts was performed to compare utilities for Hgb more than 14 g/dl to those with Hgb less than 14 g/dl for all subjects, healthy subjects, and those with osteoarthritis, cancer, and HF.

Multiple linear regression models were used to evaluate the independent association between Hgb level (defined by the interaction term of Hgb × Hgb category) and the SF-6D, while adjusting for selected covariates mentioned above, including sociodemographic characteristics, medication use, depression, and associated disease states. Regression models were adjusted for potential confounding of baseline socio-demographic factors, body mass index, physical activity, depression, disability, associated disease states, and cohort assignment using a backward selection process. The validity of model assumptions were evaluated using analysis of residuals. R^2, Akaike information criteria, and bayesian information criteria were used to evaluate the goodness of fit for the model. Confounders had to change odds ratio by 10% to be used in our final adjusted models. All *P* values were calculated with two-sided significance level of 0.05.

Adjusted least-squares means were calculated based on the regression analyses. Mean values for the SF-6D utility weights were plotted against Hgb level for the sample as a whole as well as separately for those with HF, cancer, osteoarthritis, or "healthy" (not having HF, cancer, or osteoarthritis as self-identified on the WHI instrument, and having a comorbidity index of zero as defined by the WHI-modified Charlson Index) [20].

Using longitudinal data, the relationship between the change in Hgb values and the change in SF-6D utility weights was examined. Multiple linear regression was used to evaluate the independent association between a 2 g/dl drop in Hgb compared to no loss and change in SF-6D, while adjusting for baseline Hgb group; body mass index; education level; race/ethnicity; age; exercise level; depression; self-reported history of diabetes, disability, any hospitalizations duirng past 2 years, stroke/myocardial infarction, or cancer (if appropriate); and NSAID use. The 2 g/dl drop in Hgb was chosen based on previous defination of clinically important blood loss [3] and clinical trial evidence of significant difference in physical functioning [21].

Table 1 – Baseline characteristics of postmenopausal women participants.

Variable	
No. of subjects	158,257
Age (mean y ± SD)	63.2 ± 7.23
Race (%)	
White	82.59
African American	8.97
Hispanic	4.01
Asian/Pacific Islander	2.59
Other	1.84
Education (%)	
<High school	1.66
High school	20.96
College	37.92
>College	39.46
Current smoking (%)	7.00
Physical activity (mean MET h/wk ± SD)	12.44 ± 13.73
Body mass index (mean ± SD)	27.97 ± 5.93
Disabled (%)	2.06
Lupus (%)	0.43
Osteoarthritis (%)	42.16
Diabetes (%)	4.40
Liver disease (%)	2.34
Cancer (%)	9.52
Congestive heart failure (%)	1.24
Myocardial infarction or stroke (%)	3.42
Service use	
Hospitalized overnight in past 2 years (%)	14.99
Nonsteroidal anti-inflammatory drug use (%)	18.55
Acetaminophen use (%)	8.50

SD, standard deviation.

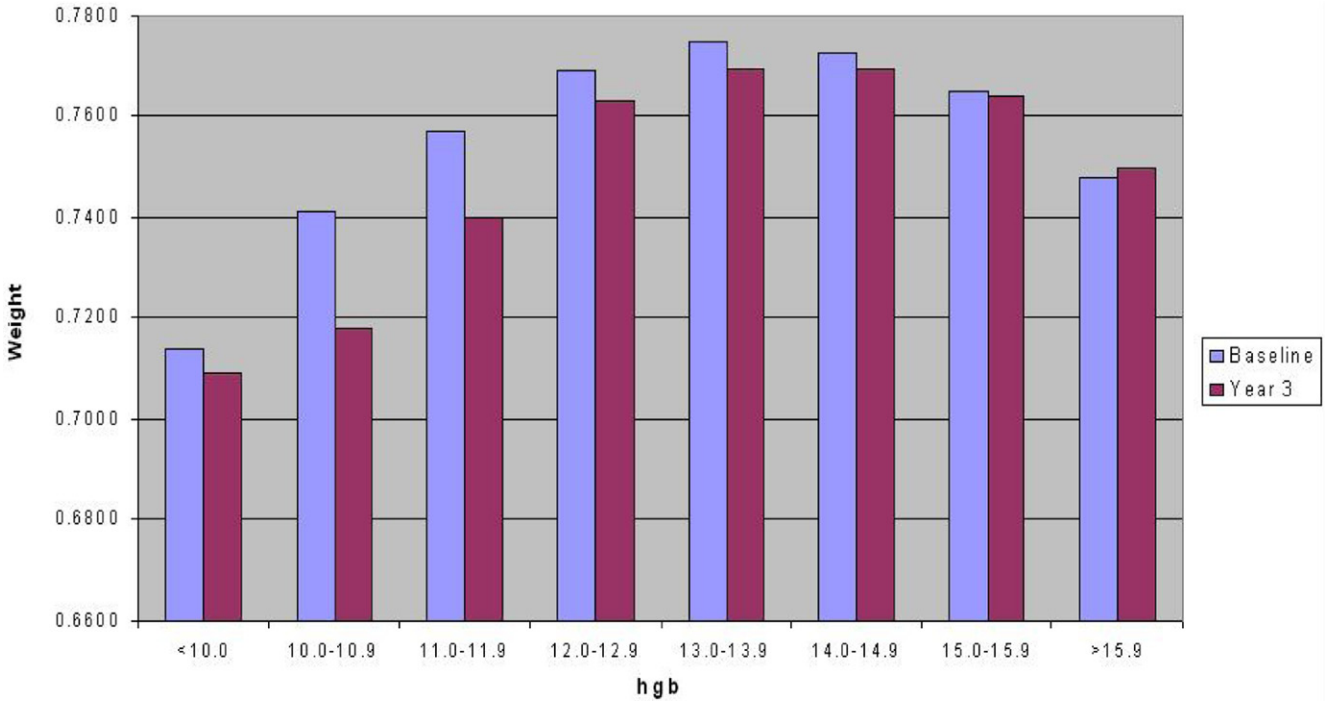

Fig. 3 – Unadjusted Short Form-6D utility weights by hemoglobin (Hgb) level at baseline and year 3.

All data analyses were performed using SAS version 9.1.3 (2004; SAS Institute, Inc., Cary, NC).

Results

From the 161,808 women in WHI, we excluded women with missing or out of the physiologic range Hgb levels (n = 2152), and those with certain medical conditions that may lead to anemia unrelated to potential blood loss such as sickle cell anemia or chronic kidney disease (n = 1399). This left 158,257 women to be included for the cross-sectional analysis (Fig. 2). The baseline characteristics of the women are presented in Table 1. The sample included in these analyses has an average age 63 years, is mostly white (82.6%), and nearly three-quarters is college educated. The most frequently reported disease was osteoarthritis (47.2%). Just under 10% reported having had cancer. Fifteen percent of women have had a hospitalization during the past year. Less than 20% use NSAIDs.

Figure 1 shows the cross-sectional relationship of covariate adjusted mean utility weights for the entire baseline sample, those who were "healthy" and the women with osteoarthritis, HF, and cancer within WHI by Hgb levels. As might be expected, those "healthy" women without documented chronic disease had the highest levels of utiliity across all levels of Hgb. Women with HF had the lowest health utilities, with sequentially higher utilities for osteoarthritis, history of cancer, and the entire cohort. In addition, for each gram of Hgb below 14 g/dl the health utilities were lower ($P < 0.0001$).

Table 2 – Adjusted* average change in participants' Short Form-6D (SF-6D) response.

Participant	Hemoglobin level change	n	P loss vs. no loss	Change in SF-6D	
				Mean (standard error)	P (H_0: x = 0)
All eligible participants	Loss	1064	<0.0001	−0.0394 (0.004014)	<0.0001
	No Loss	63,097		−0.0092 (0.002745)	0.0008
Healthy participants	Loss	254	<0.0001	−0.0158 (0.008651)	0.0687
	No Loss	21,230		0.0155 (0.006166)	0.0117
Heart failure participants	Loss	34	0.1671	−0.0217 (0.022030)	0.3242
	No Loss	724		0.0041 (0.014890)	0.7812
Cancer participants	Loss	164	<0.0001	−0.0538 (0.010340)	<0.0001
	No Loss	8414		−0.0102 (0.007049)	0.1477
Osteoarthritis participants	Loss	511	<0.0001	−0.0335 (0.005764)	<0.0001
	No Loss	27,025		−0.0070 (0.003830)	0.0694

* Estimates adjusted as follows: all eligible, heart failure, cancer, osteoarthritis: adjusted for baseline hemoglobin group, body mass index, education level, race/ethnicity, age, exercise level, depression, and self-reported history of diabetes, rheumatoid arthritis (not on treatment), disability, any hospitalizations in past 2 y, stroke or heart attack, cancer, and nonsteroidal anti-inflammatory drug use. Healthy: adjusted for baseline hemoglobin group, body mass index, education level, race/ethnicity, age, exercise level, depression, disability, any hospitalizations in past 2 years, and nonsteroidal anti-inflammatory drug use.

Table 3 – Regression analysis of the relationship between all covariates and the change in Short Form-6D response among all subjects.

Variable	Level	Coefficient	P
Intercept		0.0298	<0.0001
Hemoglobin change group	Loss	−0.03017	<0.0001
	No Loss	Reference	
Age		−0.00073	<0.0001
Race	Other	−0.00507	0.1488
	American Indian or Alaskan Native	0.00201	0.7587
	Asian or Pacific Islander	−0.00211	0.3598
	Black or African-American	0.00321	0.0548
	Hispanic/Latino	−0.00132	0.5851
	White (not of Hispanic origin)	Reference	
Education level	<High school	0.005496	0.1916
	High school	−0.00276	0.0135
	Some college	−0.00261	0.0036
	College	Reference	
Body mass index category	<25	0.003496	0.3728
	25–29.9	0.008325	<0.0001
	30–34.9	0.006589	<0.0001
	35–39.9	0.003069	0.0757
	>40.0	Reference	
Diabetes with medications	No	0.005072	0.0267
	Yes	Reference	
Disabled	No	−0.00526	0.0978
	Yes	Reference	
Rheumatoid arthritis without medications	No	0.002866	0.1288
	Yes	Reference	
Hospitalized in past 2 y	No	−0.00258	0.0218
	Yes	Reference	
Exercise level (METS)		−0.00006	0.0268
Depression score		0.07191	<0.0001
Stroke or heart attack	No	0.004987	0.03
	Yes	Reference	
Cancer diagnosis	No	0.002389	0.0413
	Yes	Reference	
Nonsteroidal anti-inflammatory drug use	No	−0.00366	0.0004
	Yes	Reference	
Baseline hemoglobin group	<12 mg/dl	0.000244	0.897
	12–13.9 mg/dl	−0.00005	0.9551
	>14.0 mg/dl	Reference	
Fit statistics	R^2	0.0140	

Longitudinal analyses limited the sample to the women who had valid Hgb and utility weight values at baseline and year 3 (n = 68,839). Only those women with nonmissing values for the covariates were used in the multivariate analyses (n = 64,161).

Utility weights were calculated using year 3 data and compared to baseline data. Figure 3 presents the average baseline and year 3 utility weights for year 3 and baseline by Hgb. Subjects with baseline Hgb in the anemic range had larger declines in utility than those with normal or high levels.

Table 2 demonstrates the adjusted mean change in SF-6D by the Hgb change group (loss vs. no loss) for all eligible participants in the WHI sample. Those women who lost 2 g Hgb or more between baseline and year 3 had a statistically significant decline in SF-6D during the 3-year period ($P < 0.0001$). This decline in the SF-6D (−0.0394) was also clinically significant, given a MCID level of 0.025 for the SF-6D measure [17]. A comparison of the change in SF-6D between women who lost 2 g Hgb or more and those with no loss in Hgb level shows the difference is statistically significant (−0.0394 vs. −0.0092, $P < 0.0001$) and is also clinically meaningful.

Table 2 also shows the adjusted change in SF-6D by Hgb change group for four separate cohorts: healthy (no self-reported disease), and self-reported HF, cancer, and osteoarthritis.

The loss of 2 g/dl Hgb was associated with a statistically significant ($P < 0.05$) as well as a clinically meaningfully decline in SF-6D in all participants as well as in the group of participants with cancer and osteoarthritis, respectively (Table 2). A comparison of the change in SF-6D between those who lost 2 g/dl Hgb or more and the no loss group shows a statistically significant difference in healthy participants ($P < 0.0001$), participants with osteoarthritis ($P < 0.001$), and participants with cancer ($P < 0.0001$) but not in participants with HF ($P = 0.1671$).

Tables 3 and 4 show the relationship between all covariates and the change in SF-6D among all subjects (Table 3) and in each cohort (Table 4). In addition to the Hgb loss, age and depression score are significantly associated with the change in SF-6D among all study subjects, healthy participants, participants with osteoporosis and participants with cancer, but not in participants with HF.

Discussion

Based on a large population of postmenopausal women, our study shows that lower levels of Hgb (up to 14 g/dl) are associated with lower health utility among all participants and also in the subgroup of participants with self-report osteoarthritis, cancer, and HF. For

Table 4 – Regression analysis of the relationship between all covariates and the change in Short Form-6D response in each cohort.

		Healthy		Arthritis		Cancer		Heart failure	
Variable	Level	Coefficient	P	Coefficient	P	Coefficient	P	Coefficient	P
Intercept		0.06147	<0.0001	0.0328	0.0001	0.04845	0.0013	−0.04227	0.3381
Hemoglobin change group	Loss	−0.03129	<0.0001	−0.02652	<0.0001	−0.04364	<0.0001	−0.02587	0.1671
	No Loss	Reference		Reference		Reference		Reference	
Age		−0.00074	<0.0001	−0.00073	<0.0001	−0.00086	<0.0001	0.000234	0.6905
Race	Other	−0.00477	0.4202	−0.00276	0.6166	−0.00093	0.9266	−0.00877	0.7927
	American Indian or Alaskan Native	0.02609	0.0513	0.01091	0.2617	−0.01958	0.2867	0.03162	0.4389
	Asian or Pacific Islander	−0.00079	0.8144	−0.00314	0.4592	−0.0008	0.9213	0.01681	0.5991
	Black or African-American	0.00123	0.6691	0.003675	0.1566	−0.00003	0.9956	0.01419	0.2451
	Hispanic/Latino	−0.00587	0.1296	0.001813	0.6500	−0.02025	0.0095	0.006248	0.8015
	White (not of Hispanic origin)	Reference		Reference		Reference		Reference	
Education level	<High school	0.02472	0.0040	0.001652	0.7829	0.01181	0.3289	−0.0013	0.9533
	High school	−0.00154	0.4206	−0.00259	0.1288	−0.0031	0.3174	−0.00515	0.6213
	Some college	−0.00462	0.0018	−0.00157	0.2641	−0.0016	0.5180	−0.00043	0.9628
	College	Reference		Reference		Reference		Reference	
Body mass index category	<25	0.002034	0.7537	0.003882	0.5673	0.004891	0.6434	0.02975	0.3506
	25–29.9	0.004742	0.1377	0.009288	<0.0001	0.01007	0.0174	0.01704	0.1672
	30–34.9	0.001521	0.6361	0.009818	<0.0001	0.007529	0.0736	0.007111	0.5457
	35–39.9	0.002996	0.3982	0.00359	0.1352	0.004618	0.3127	0.005735	0.6513
	>40.0	Reference		Reference		Reference		Reference	
Diabetes with medications	No	—		0.004794	0.1393	0.00036	0.9491	0.003661	0.7423
	Yes	—		Reference		Reference		Reference	
Disabled	No	−0.01526	0.1390	−0.00333	0.4298	−0.00119	0.8725	−0.00757	0.5789
	Yes	Reference		Reference		Reference		Reference	
Rheumatoid arthritis without medications	No	—		—		0.005855	0.2158	0.001043	0.9287
	Yes	—		—		Reference		Reference	
Hospitalized in past 2 y	No	−0.00191	0.4309	−0.00143	0.3733	−0.00984	0.0002	0.003487	0.6480
	Yes	Reference		Reference		Reference		Reference	
Exercise level (METS)		−0.00004	0.4048	−0.00009	0.0661	−0.00013	0.1178	0.000093	0.7820
Depression score		0.09791	<0.0001	0.06486	<0.0001	0.0615	<0.0001	0.03672	0.1390
Stroke or heart attack	No	—		0.001722	0.5948	−0.00424	0.4403	0.01289	0.1022
	Yes	—		Reference		Reference		Reference	
Cancer diagnosis	No	—		−0.00092	0.5963	—		0.002069	0.8361
	Yes	—		Reference		—		Reference	
Nonsteroidal anti-inflammatory drug use	No	−0.00517	0.0158	−0.00289	0.0390	−0.00252	0.3666	−0.00658	0.5132
	Yes	Reference		Reference		Reference		Reference	
Baseline hemoglobin group	<12 mg/dl	0.000201	0.9514	0.000353	0.9023	0.004388	0.3841	0.008427	0.5510
	12–13.9 mg/dl	−0.00229	0.1233	0.000712	0.6056	0.00194	0.4325	0.000447	0.9583
	>14.0 mg/dl	Reference		Reference		Reference		Reference	
Fit statistics	R^2	0.0169		0.0131		0.0184		0.0182	

subjects with 2 g/dl Hgb decrease or more, there is a statistically significant and clinically meaningful decrement in health utility among all participants as well as in those with cancer and osteoarthritis, whereas the HF group had too few women with a change in SF-6D to be significant. A comparison of change in SF-6D between those who lost 2 g/dl Hgb and the no-change group shows a statisically significant difference in all participants. The significant difference was also observed in those with osteoarthritis and with cancer. These findings demonstrate the statistically significant and clinically important effect that changes in Hgb level may have on health utility in postmenopausal women. The effect may be more important for those with chronic medical conditions who may already be experiencing a lower QoL.

Findings from this study are consistent with several previous studies that used other patient-reported QoL measures to assess the potential effects associated with Hgb change in people with osteoarthritis or cancer. In a study of relationship between Hgb in patients with rheumatoid arthritis and physical disability assessed by a health assessment questionnaire, Han et al. [22] found lower levels of baseline Hgb were associated with more severe physical disability and improvement in Hgb level after treatment was an independent contributor to the improvement of physical function.

In a longitudinal analysis based on data from 14 randomized clinical trials, Strand et al. [21] found that patients with arthritis with minimal to no change in Hgb level reported statistically significant and clinically meaningful improvements in all eight domains of SF-36 in both women and men. In contrast, subjects with Hgb decreases of 2 g/dl or more did not report clinically meaningful nor statistically significant improvements in most domains of SF-36. A comparison of changes in SF-36 scores demonstrated statistically significant and clinically meaningful differences in physical function in both women and men, and in

role physical in men between subjects with Hgb decrease greater than 2 g/dl and those with minimal to no change in Hgb level.

In patients with cancer, anemia as a significant complication of disease itself and cancer therapies has been found to be able to cause fatigue, dizziness, and dyspnea that can affect health-related QoL [23]. Potentially, therapies that result in significant increase in Hgb level may improve cancer patients' QoL significantly [24,25].

This study represents the first that assesses health utility associated with changing levels of Hgb in patients with osteoarthritis. In patients with cancer, health utility associated with different levels of Hgb has been previously documented. Consistent with our findings, Lloyd et al. [5] showed a decrement in health utility scores in line with worsening anemia. Unlike the Lloyd study that looked at a sample of patients with cancer, our study assesses health utility based on a population of postmenopausal women. Population-based utility measures may be more useful for informing resource allocation and decision-making on a societal level.

The health utility scores in our study were obtained indirectly via a generic health-related QoL questionnaire, the SF-6D. Compared to the health utility scores obtained though direct methods such as standard gamble or time trade-off, the scores from the indirect methods tend to be lower and the difference can be substantial [26]. Although the use of indirect methods for health utility measurement may have implications on resource allocations, there is no universally accepted theoretical basis on whether to choose direct or indirect methods [26].

The health utility estimates in our study can be used in future economic modeling studies that evaluate cost-effectiveness of interventions to mitigate blood loss. These estimates also have implications for future decision making regarding medication management of patients with osteoarthritis. Our analyses suggest that 2 g/dl Hgb level decrease is associated with statistically significant and clinically meaningful decrement in health utility in participants with osteoarthritis. Because patients with osteoarthritis frequently require anti-inflammatory therapy that may lead to significant gastrointestinal toxicity-associated blood loss, it is important to consider this when choosing treatments for osteoarthritis.

This study was subject to several limitations. First, this was an observational study in which study subjects were not randomized to different therapies affecting Hgb levels and therefore a causal relationship cannot be inferred. Although we have tried to adjust for various factors that may have confounded the relationship between Hgb and health utility, it is possible that unmeasured confounders may have affected our results. Second, our study was limited to postmenopausal women and study results can not be generalized to younger women or to men. Third, in this study, a difference of 0.025 in SF-6D was considered to be MCID. This cutoff score is not universally accepted and there have been debates about the MCID for SF-6D. Finally, the disease status in this study was obtained by self-report, not confirmed by physician diagnosis.

Conclusions

This study provides estimates of health utility associated with different levels of Hgb among all postmenopausal women and also in those with chronic conditions, including cancer, osteoarthritis, and HF. The estimates will be useful for future economic evaluations to assess cost-effectiveness of interventions to mitigate blood loss. This study also demonstrates significant association between Hgb and health utility in all postmenopausal women as well as in those with selected chronic conditions. For subjects with a 2-g/dl Hgb decrease, there is a statistically significant and clinically meaningful decrement in health utility. These findings, consistent with previous studies, raise concerns about potential consequences associated with Hgb level decrease and indicate a need for cost-effective treatments to mitigate blood loss.

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