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Research Article

The Relative Importance of Biomarkers for Body Iron Storage and Socio-Demographic Factors on all-Cause Mortality of Adults

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Abstract

Background

The relationship between biomarkers of body iron storage and adult mortality has not been clearly defined. This study investigated the hypothesis that this may be due to the fact that the effects of these biomarkers were relatively small when compared to socio-economic factors.

Patients and Methods

Public use National Health and Nutrition Examination Survey (NHANES III) data were used. NHANES III complex probabilistic household adult, laboratory and mortality data were merged. Specialized survey analysis software was used. Only sample persons examined in the Mobile Examination Center were included in this study.

Results

There were 3432 sample persons with a mean follow up of 170 months. After multivariate analysis, the significant variables, odds ratios (95% confidence intervals) were: age 1.0089 (1.0078 - 1.0100); female sex (relative to male sex) 0 .716 (0.485-1.058); poverty income ratio 0.808 (0 .739 - 0 .883); drinking hard liquors 1.0131 (1.0034 - 1.0229); and serum ferritin concentration 1.000846 (1.000011- 1.001681).

Conclusion

After adjusting for covariates socio-demographic factors were more important than iron storage biomarkers as predictors of all cause mortality in adults. Further investigation may clarify if iron status biomarkers are important in subsets of survey participants.

Keywords: NHANES III; Serum Iron Biomarkers; Socio-Demographic Status; All Cause Mortality; Adults

Introduction

Too high or too low body iron storage status has been linked to cardiovascular health and all cause mortality. Iron deficiency found in developing countries was associated with higher mortality risk [1]. Iron deficiency was also associated with community dwelling adults and self reported heart failure [2]. High body iron storage status has been associated with associated with increased risk myocardial infarction secondary to increased lipid oxidation [3]. Iron storage in body was linked to higher cancer risk because it was a micronutrient need for tumor growth [4]. However, association between iron status and all cause mortality has been conflicting [5]. This study used data from National Health and Nutrition Examination Survey (NHANES), as a part of a series screening for potential chemicals with beneficial health effects, to take advantage of the vastness of the public use NHANES III data to test if socio-demographic, health status factors may be confounding the effects of iron biomarkers' effects on mortality of US adults.

Materials and Methods

NHANES and NHANES III

NHANES is a major program of National Center of Health Statistics (a part of Center of Disease Control (CDC) of United States of America) started in 1971. NHANES III is a national study based on a complex, multi-stage probability sampling design. For details of NHANES data and statistical guidance as well as their analysis examples see NHANES website [6]. In brief, NHANES studies were approved by CDC internal institutional review boards. The public use data are made available to the public and researchers. The NHANES sample weights were calculated to represent non-institutionalized general US population to account for non-coverage and non-response. These patients were interviewed at home and examined in mobile examination centers (MEC). This eliminated the cofounding effects of sample persons being too frail, too young or old to go to the MEC for examinations. In this study, NHANES III (conducted between1988–1994) household adult data file was merged with NHANES III laboratory data and the NHANES III linked cancer mortality data.

NHNAES III linked mortality data

NHANES III participants were followed passively until December 31, 2006 for their mortality data. Detailed information about the data and analysis guidelines are available at their website [7]. In brief, probability matching was used to link NHANES III with National Death Index for vital status and mortality, age 90 years old was censored because they contribute little in person years. NHANES used multiple sources including the use of death certificates and with the National Death Index to ascertain vital status and cause of death (UCOD_113).

Statistical analysis

NHANES III employed a complex sampling strategy and analysis [8-11]. Matlab programs (posted on Matlab File Exchange) were developed to convert SAS files provided by NAHNES to STATA programs to download NHANES III data files for further analysis. Specialized survey software is needed for NHANES complex data analysis [12]. STATA 12 (College Station, TX) was among those recommended by CDC to analyze the complex NHANES data and was used in this study. The sampling weight used was WTPFEX6 because only the sample persons had examinations in the MEC were included in this study, SDPPSU6 was used for the probability sampling unit (PSU) and SDPSTRA6 was used to designate the strata for the STATA survey commands. STATA scripts were written for this analysis, and will be submitted for publication separately. Univariate and multivariate logistic regressions [13] were used to study the relationship between FEPSI (serum iron concentration in umol/L), TIPSI (serum total iron binding capacity in umol/L), FRPSI (serum ferritin concentration in ug/L), PXP (serum transferring saturation in %) and all cause in adults (17 years or older). The status of mortality was coded as a binary outcome (1= death, 0 = otherwise). Linearized Taylor Standard Error estimation was used. The covariates and the corresponding NHANES III codes used were: MXPAXTMR (age at the MEC final examination in months), HSSEX (sex, _IHSSEX_1 = male, female as the reference group when applicable), HAM6S (weight in lbs without clothes), DMPMETRO (urban rural residence status), _IDMPMETRO_2 (rural residence, urban residence was used as the reference group), DMARETHN (race and ethnicity, _IDMARETHN_2 = non-Hispanic black, _IDMARETHN_3 = Mexican Americans, _IDMARETHN_4 = others, non-Hispanic white was used as the reference group), DMPPIR (poverty index ratio), HAN6JS (alcohol consumption, number of hard liquor drinks per month), and HAR4S (smoking, number cigarettes per day). For STATA analyses, only the patients without missing values for all of WTPFEX6, SDPPSU6, SDPSTRA6, MXPAXTMR, HSSEX, DMPMETRO, HAM6S, DMARETHN, DMPPIR, HAR4S, HAN6JS, FEPSI , TIPSI, FRPSI and PXP were included in this study. Further, these additional NHANES III codes considered not eligible: HAM6S (888), HAM6S (999), DMPPIR (888888), the numerator of DMPPIR was the midpoint of the observed family income category in the Family Questionnaire variable:HFF19R, and the denominator was the poverty threshold, the age of the family reference person, and the calendar year in which the family was interviewed, HAR4S (666), HAR4S (777), HAR4S (888), HAR4S (999), HAN6JS (888), HAN6JS (999), not in BMI > 15 & BMI < 50, FEPSI (88888), TIPSI(888888), FRPSI(8888), PXP(8888), youth sample persons and incomplete mortality data. A total of 3432 sample persons with complete data were analyzed in this study.

Results

The general characteristics of the NHANES III linked mortality data were as follows. There were 20024 cases in NHANES III linked mortality data file included in this study. 13944 cases were not available in the public use file to protect the privacy of youth subjects. 26 cases in the NHANES III linked dataset did not have mortality data. All cause mortality (5291 deaths out of 33994 subjects, uod_113 codes were used to determine the cause of death) was used as the binary outcomes for this analysis. The NHANES III adult data file and the NHANES III linked mortality file were merged according to the SEQN number provided by NHANES III to uniquely identify the cases. All the results were obtained by using survey command taking into account the primary sampling unit and stratification variables and the weights assigned to the sample persons examined in the MEC. Thus these results were representative of the US population.

There were 3432 sample persons (Table 1) had complete data and were used in this analysis. The univariables (S.E.) were: the risk of death (S.E.) (Indicator Death), 0.156 (0.140 - 0 .173) ; body mass index (BMI), 25.234 (24.937 - 25.532); age (MXPAXTMR), 474.121 (464.881 - 483.361); sex (HSSEX, male = 1, female = 2), 1.455 (1.439 - 1.472) ; urbanicity (DMPMETRO, urban = 1, rural = 2), 1.570 (1.466 - 1.675) ; poverty income ratio (DMPPIR), 2.680 (2.546 -2.814) ; smoking (cigarettes per day) (HAR4S), 19.838 (18.950 - 20.726) ; drinking hard liquors (drinks per month) (HAN6JS), 2.796 (2.235 - 3.358) ; follow up in months (permth_exm) 169.982 (164.170 - 175.796) ; Serum iron concentration (umol/L) (FEPSI), 16.881 (16.532 - 17.231); serum total iron binding capacity (umol/L) (TIBC, TIPSI) , 63.481 (62.691 -64.270); Serum ferritin (ug/L) (FRPSI) 127.476 (121.215 - 133.736); and serum transferring saturation (%) (PXP), 27.222 (26.559- 27.885).

	Linearized			
	Mean	Std. Err.	[95% Conf.	Interval]
Indicator Death	.156	.008	.140	.173
BMI	25.234	.148	24.937	25.532
MXPAXTMR	474.121	4.598	464.881	483.361
HSSEX	1.455	.008	1.439	1.472
DMPMETRO	1.570	.052	1.466	1.675
DMARETHN	1.350	.031	1.288	1.413
DMPPIR	2.680	.067	2.546	2.814
HAR4S	19.838	.442	18.950	20.726
HAN6JS	2.796	.279	2.235	3.357
permth_exm	169.982	2.893	164.169	175.796
FEPSI	16.881	.174	16.532	17.231
TIPSI	63.481	.393	62.691	64.270
FRPSI	127.476	3.115	121.215	133.736
PXP	27.222	.330	26.559	27.885

Table 1. Baseline demographics, health status and body iron storage covariables of adult all cause mortality. IndicatorDeath: 0=alive, 1=dead. Linearized Taylor Standard Error estimation was used. The NHANES III codes used were: body mass index, MXPAXTMR (age at the MEC final examination), HSSEX (sex), DMPMETRO (urban rural residence status), HAM6S (weight in lbs without clothes), DMARETHN (race and ethnicity), DMPPIR (poverty index ratio), HAN6JS (alcohol consumption), HAR4S (smoking), and permth_exm (months of follow up from MEC examination). FEPSI (serum iron concentration in S.I. units), TIPSI (serum total iron binding capacity in S.I. units), FRPSI (serum ferritin concentration in S.I. units), PXP (serum transferring saturation in S.I. units), n = 3432 samples.

For univariate analysis, the significant univariates (Table 2), odds ratios (95% confidence intervals) were: age 1.00866 (1.00760 - 1.00971) ; poverty income ratio 0.914 (0.852 - 0.980); drinking hard liquors 1.0163 (1.000626 - 1.032208); Serum iron concentration 0.969 (0.951 - 0 .988); total iron binding capacity 0.989 (0.979 - 0 .999); serum ferritin concentratin 1.00211 (1.00134 - 1.00287); and serum transferin saturation 0.987 (0.977 - 0 .998). Two models were obtained from multivariate, model B was obtained from model A after stepwise elimination. Only the least significant predicators were removed from model A so as not to potentially removing a useful predictor (to minimize type II errors [14]) in building model B. The significant variables (Table 3, model B), odds ratios (95% confidence intervals) were: age 1.0089 (1.0078 - 1.0100); female sex (relative to male sex) 0 .716 (0.485-1.058); poverty income ratio 0.808 (0 .739 - 0 .883); drinking hard liquors 1.0131 (1.0034 - 1.0229); and serum ferritin concentration 1.000846 (1.000011 - 1.001681).

	Linearized					
Indicator Death	Odds Ratio	Std. Err.	t	P>|t|	[95% Conf.	Int]
BMI	1.027	.014	1.93	0.060	.999	1.055
MXPAXTMR	1.009	.0005	16.54	0.000	1.008	1.010
HSSEX	.858	.104	-1.27	0.210	.673	1.093
DMPMETRO	1.102	.129	0.83	0.409	.871	1.395
DMARETHN	1.019	.073	0.26	0.794	.882	1.177
DMPPIR	.914	.032	-2.57	0.013	.852	.980
HAN6JS	1.016	.008	2.09	0.042	1.0006	1.032
HAR4S	1.010	.006	1.81	0.076	.999	1.021
FEPSI	.969	.009	-3.33	0.002	.951	.988
TIPSI	.989	.005	-2.16	0.036	.979	.999
FRPSI	1.002	.0004	5.52	0.000	1.001	1.003
PXP	.987	.005	-2.47	0.017	.977	.998

Table 2. Univariate analysis of demographics, health status and body iron storage covariables of adult all cause mortality. IndicatorDeath: 0=alive, 1=dead. Linearized Taylor Standard Error estimation was used. The NHANES III codes used were: body mass index, MXPAXTMR (age at the MEC final examination), HSSEX (sex), DMPMETRO (urban rural residence status), HAM6S (weight in lbs without clothes), DMARETHN (race and ethnicity), DMPPIR (poverty index ratio), HAN6JS (alcohol consumption), HAR4S (smoking), and permth_exm (months of follow up from MEC examination). FEPSI (serum iron concentration in S.I. units), TIPSI (serum total iron binding capacity in S.I. units), FRPSI (serum ferritin concentration in S.I. units), PXP (serum transferring saturation in S.I. units), n = 3432 samples.

Model A:

Indicator Death	Odds Ratio	Linearized Std.Err.	t	P>|t|	[95% Conf.	Int]
BMI	1.023	.015	1.59	0.118	.994	1.054
MXPAXTMR	1.009	.001	16.30	0.000	1.008	1.010
_IHSSEX_2	.704	.137	-1.81	0.077	.476	1.040
_IDMPMETRO_2	1.039	.132	0.30	0.765	.805	1.342
_IDMARETHN_2	1.331	.190	2.00	0.051	.998	1.774
_IDMARETHN_3	.651	.155	-1.80	0.078	.403	1.052
_IDMARETHN_4	.723	.214	-1.09	0.279	.398	1.312
DMPPIR	.809	.0365	-4.69	0.000	.739	.886
HAN6JS	1.013	.005	2.95	0.005	1.004	1.023
FEPSI	.919	.054	-1.44	0.155	.817	1.033
TIPSI	1.026	.014	1.88	0.066	.998	1.055
FRPSI	1.0008	.0004	1.86	0.069	1.000	1.002
PXP	1.042	.037	1.16	0.251	.970	1.119
_cons	.0003	.0003	-8.11	0.000	.000	.002

Model B:

Indicator Death	Odds Ratio	Linearized Std. Err.	t	P>|t|	[95% Conf.	Int]
BMI	1.023	.015	1.58	0.121	.994	1.053
MXPAXTMR	1.009	.0005	16.34	0.000	1.008	1.010
_IHSSEX_2	.716	.139	-1.72	0.092	.485	1.058
_IDMARETHN_2	1.314	.188	1.91	0.063	.985	1.753
_IDMARETHN_3	.650	.158	-1.77	0.082	.399	1.059
_IDMARETHN_4	.717	.206	-1.16	0.253	.402	1.278
DMPPIR	.808	.036	-4.83	0.000	.739	.883
HAN6JS	1.013	.005	2.72	0.009	1.003	1.023
FEPSI	.982	.010	-1.81	0.076	.962	1.002
TIPSI	1.010	.010	1.07	0.288	.991	1.030
FRPSI	1.001	.0004	2.04	0.047	1.00001	1.002
_cons	.0009	.0008	-7.71	0.000	.0002	.006

Table 3. Multivariate analysis of socio-demographic factors, serum albumin and globulin levels and all cause mortality. Indicator Death: 0=alive, 1=dead. Linearized Taylor Standard Error estimation was used. The NHANES III codes used were: BMI (body mass index), HSSEX (_IHSSEX2 = female, using male as the reference group), MXPAXTMR (age at the MEC final examination), HAM6S (weight in lbs without clothes), DMPMETRO (urban rural residence status, _IDMPMETRO_2 = rural residence, urban residence used as the reference group), DMARETHN (race and ethnicity, _IDMARETHN_2 = non-Hispanic black, _IDMARETHN_3 = Mexicans, _IDMARETHN_4 = others, non-Hispanic white used as the reference group), DMPPIR (poverty index ratio), HAN6JS (alcohol consumption), and HAR4S (smoking)). FEPSI (serum iron concentration in S.I. units), TIPSI (serum total iron binding capacity in S.I. units), FRPSI (serum ferritin concentration in S.I. units), PXP (serum transferring saturation in S.I. units), n = 3432 samples. Model B was obtained from backward elimination of model A

Discussion

Iron has been associated with oxidative stress. Iron storage in body is associated with cancer risk, cardiovascular disease risk, and all-cause mortality risk [2,4]. However, the association between iron status and all cause mortality has been conflicting [5], and was the subject of this investigation. In particular, this study examined if the socio-demographic factors were much more important than iron biomarkers in predicting mortality of US adults. There were 3432 sample persons (Table 1) had complete data and were used in this analysis. The univariables were (Table 2): age, poverty income ratio, drinking hard liquors, serum iron concentration, total iron binding capacity, serum ferritin concentration, and serum transferrin saturation. Thus the univariate analysis revealed that all four iron status biomarkers tested in this study were significant univariates. After eliminating the less significant variables in Table 3 model A, the significant variables (Table 3 model B) and the respective odds ratios were age 1.0089 (1.0078 - 1.0100) , poverty income ratio 0.808 (0 .739- 0 .883), drinking hard liquors 1.0131 (1.0034 - 1.0229); and serum ferritin concentration 1.000846 (1.000011 - 1.001681). Previous studies have found racial disparities [15] [16] and the adverse effects of smoking and drinking [17]. After adjustment under multivariate analysis, this study found socio-demographic factors had significantly higher impact in terms of odds ratios and p-values then the serum iron biomarkers. Although serum ferritin concentration was statistically significant (Table 3, model B), the magnitude of the odds ratio indicated that the effect of ferritin was no significant[14]. This is consistent with earlier studies. Previous study found an association between transferrin saturation and all cause and cancer mortality in US adults but not serum ferritin concentration [18]. Serum transferring concentration was found to be significant predictor of mortality [3,19,20]. Although, serum transferrin level was a significant predictor of mortality as a univariate (Table 2), it was not a significant predictor after adjusting for other socio-demographic covariates (Table 3, model A and model B). Unlike most previous studies, this study analyzed serum ferritin, transferin, free iron concentrations and total iron binding capacity as continuous variables in an effort improve the power of detecting significant effects. Iron storage was found to be correlated with sex, age and race [21]. Alcohol has been reported to interfere with iron metabolism and confound the effects of serum iron biomarkers [22]. Although this study found no significant effects of iron storage biomarkers in predicting mortality of US adults after adjusting for significant socio-economic factors, further investigation is underway to study if iron biomarkers there are important associations between serum biomarkers and mortality in subset of survey participants.

Conflict of Interest

No conflict of interest.

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