

## **HRS Documentation Report**

### ***VBS 2016 Supplemental File: Cytokines, Vitamin D, and IGF 1 from the 2016 Venous Blood Study 2016 Health and Retirement Study***

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## Introduction

This document contains information on 5 cytokines, Vitamin D, and IGF-1 that were included as part of the HRS 2016 Venous Blood Study.

Procedures for collection, assay, and descriptions of other blood-based variables are included in the documentation - *Venous blood collection and assay protocol in the 2016 Health and Retirement Study*. <https://hrs.isr.umich.edu/publications/biblio/9065>

## Subsample Weights

*Sample Weights for the 2016 Venous Blood Study – Full sample (PVBSWGTR)*

Respondents with at least one valid venous blood result (VBS16VALID) were assigned a VBS weight. The weights were adjusted for the differential probabilities of participation by dividing the HRS 2016 sample weight by the predicted probability of having a valid venous blood result among community-dwelling 2016 HRS respondents born prior to 1960, excluding all members of the LBB cohort. The resulting interim weight was trimmed at the 1st and 99th percentiles and was then post stratified back to the entire 2016 HRS sample born prior to 1960 by age, sex, and race/ethnicity. Analysts should use *PVBSWGTR* to weight the data included with this release.

## Assays

### 1. VBS Cytokines

A. This document provides a description of the data on 5 cytokines assayed after the initial data release. The cytokines include: IL-6, IL-10, IL-1RA, sTNFR-I, TGF-  $\beta$ 1 (activated form).

**Interleukin-6 (IL-6):** IL-6 is measured in serum by an enzyme-linked immunosorbent assay (ELISA) technique using the Human Interleukin 6 Simple Plex Assay on the ELLA System from Protein Simple (San Jose, CA). The manufacturer inter-assay CV is 8.3% at a concentration of 41.5 pg/mL and 7.1% at a concentration of 1800 pg/mL. This assay has been correlated to the Quantikine ELISA Kit from R&D Systems (Minneapolis, MN) with a slope of 0.9-1.1 and an  $R^2$  value  $> 0.9$ .

**Interleukin-10 (IL-10):** IL-10 is measured in serum by a enzyme-linked immunosorbent assay (ELISA) technique using the Human Interleukin 10 Simple Plex Assay on the ELLA System from Protein Simple (San Jose, CA). The manufacturer inter-assay CV is 7.1% at a concentration of 33.2 pg/mL and 7.1 at a concentration of 1681 pg/mL. This assay has been correlated to the Quantikine ELISA Kit from R&D Systems (Minneapolis, MN) with a slope of 0.9-1.1 and an  $R^2$  value  $> 0.9$ .

**Interleukin-1 receptor antagonist (IL-1RA):** IL-1ra is measured in serum by an enzyme-linked immunosorbent assay (ELISA) technique using the Human Interleukin 1 receptor antagonist Simple Plex Assay on the ELLA System from Protein Simple (San

Jose, CA). The manufacturer inter-assay CV is 7.4% at a concentration of 27.2 pg/mL and 5.0% at a concentration of 1390 pg/mL. This assay has been correlated to the Quantikine ELISA Kit from R&D Systems (Minneapolis, MN) with a slope of 0.9-1.1 and an R<sup>2</sup> value > 0.9.

**(soluble) Tumor Necrosis Factor (sTNFR-1):** sTNFR1 is measured in serum by an enzyme-linked immunosorbent assay (ELISA) technique using the Human Tumor Necrosis Factor Receptor 1 Simple Plex Assay on the ELLA System from Protein Simple (San Jose, CA). The manufacturer inter-assay CV is 11.8% at a concentration of 19.5 pg/mL and 10.0% at a concentration of 971 pg/mL. This assay has been correlated to the Quantikine ELISA Kit from R&D Systems (Minneapolis, MN) with a slope of 0.9-1.1 and an R<sup>2</sup> value > 0.9.

**Transforming growth factor beta 1 (TGF-β1):** TGF-β1 is measured in serum by an enzyme-linked immunosorbent assay (ELISA) technique using the Human Transforming Growth Factor beta 1 Simple Plex Assay on the ELLA System from Protein Simple (San Jose, CA). The manufacturer inter-assay CV is 6.9% at a concentration of 89.9 pg/mL and 6.9% at a concentration of 5109 pg/mL. This assay has been correlated to the Quantikine ELISA Kit from R&D Systems (Minneapolis, MN) with a slope of 0.9-1.1 and an R<sup>2</sup> value > 0.9.

	Variable Name
IL-6	pIL6
IL-10	pIL10
IL-1RA	pIL1RA
sTNFR-1	pTNFR1
TGF-β1	pTGF_beta

**B. Descriptive Results (unweighted):** We coded a number of extremely high values as missing for these tables: IL-6>1000 (7 cases), IL-10>300 (2 cases), IL-1RA>12,000 (3 cases), sTNFR-1>40,000 (2 cases), TGF-β1>300,000 (1 case).

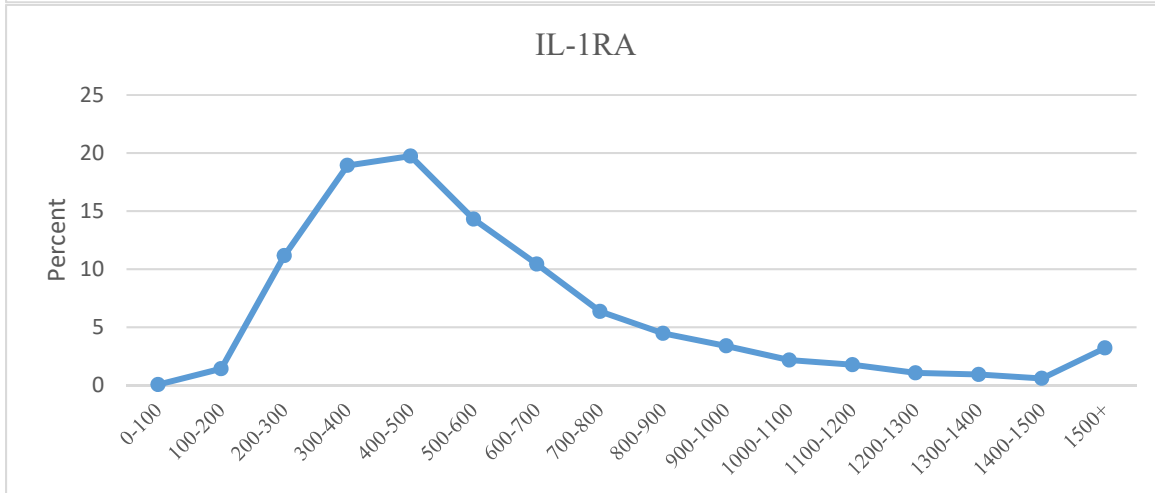
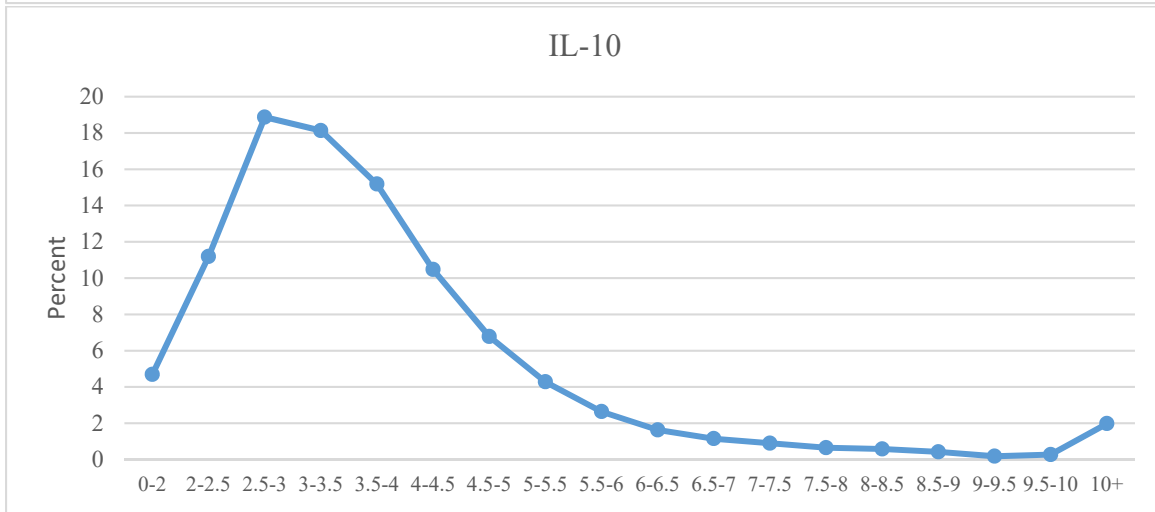
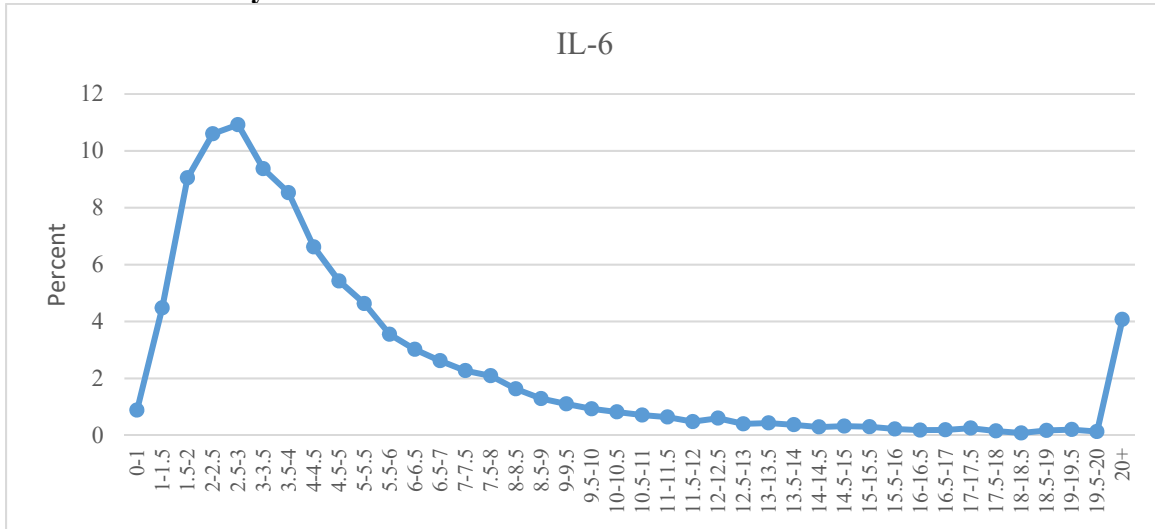
**Descriptive Measures (unweighted)**

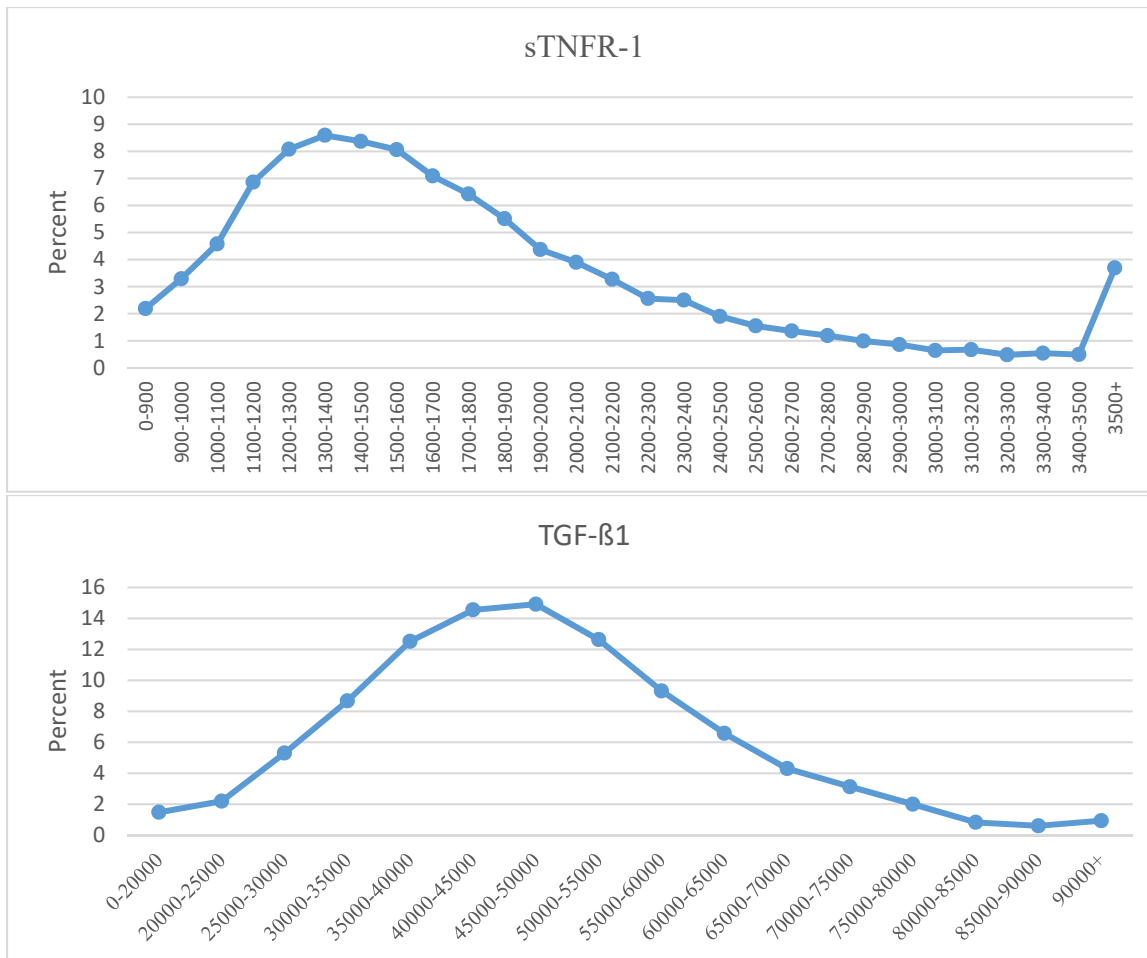
Variable	N	Mean	Std Dev	Minimum	Maximum
IL-6	9823	6.95	20.44	0.42	784.50
IL-10	9828	3.98	3.88	0.33	179.60
IL-1RA	9827	599.84	441.64	19.57	10735.90
sTNFR-1	9828	1869.17	1553.40	372.11	29734.24
TGF-β1	9827	47990.93	14663.59	449.14	149464.90

**Correlations among Cytokines (unweighted)**

<b>Variable</b>	<b>IL6</b>	<b>IL10</b>	<b>IL1ra</b>	<b>TNFR1</b>	<b>TGF beta</b>
IL-6		0.027 <.0001	0.136 <.0001	0.028 .0052	-0.023 .0219
IL-10			0.082 <.0001	0.073 <.0001	-0.009 .3756
IL-1RA				0.143 <.0001	0.063 <.0001
sTNFR-1					-0.115 <.0001
TGF-β1					

## Distributions of Cytokines





**C. Comparison of Cytokine results with other studies:** For comparison, we present HRS 2016 results alongside those from MIDUS (MIDLIFE in the United States) 2004-2009 and InCHIANTI 2001-2003.

All values are weighted for HRS, InCHIANTI and MIDUS (weight=1): Ages 56+. The HRS weight used is a preliminary version of PVBSWGTR and differs slightly from what is currently available in the Tracker file. The results presented here are for comparison purposes only.

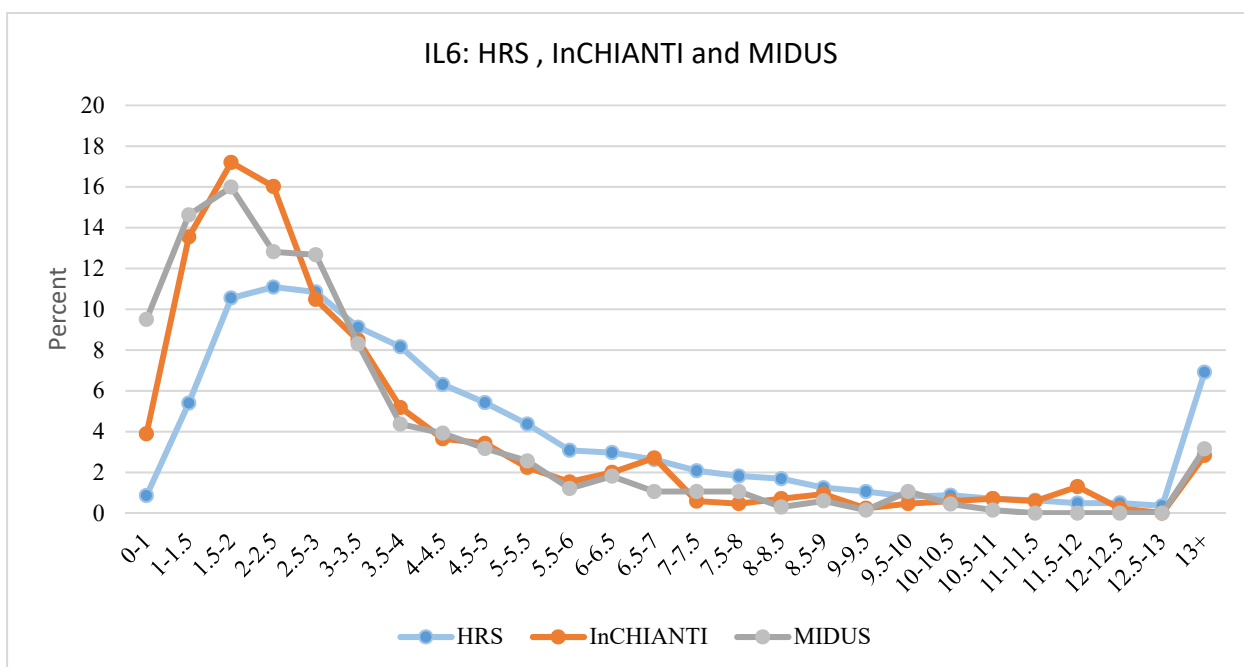
**Descriptive Results: Ages 56+ (weighted)**

	N	Mean (SD)	Median	Minimum	Maximum
<b>IL6</b>					
HRS	9084	6.65 (19.15)	3.63	0.42	641.44
MIDUS	663	3.29 (3.28)	2.40	0.31	23.00
InCHIANTI	849	3.49 (2.82)	2.48	0.55	13.00

sTNFR-1					
HRS	9089	1838.07 (1408.56)	1585.21	372.11	29734.24
InCHIANTI	849	1755.91 (866.18)	1536	654.60	7000.00

\*InCHIANTI 1998-2000: statistics provided from raw laboratory data.

### Distribution of Cytokines in HRS (2016), InCHIANTI (2001-2003) and MIDUS (2004-2009): Age 56+

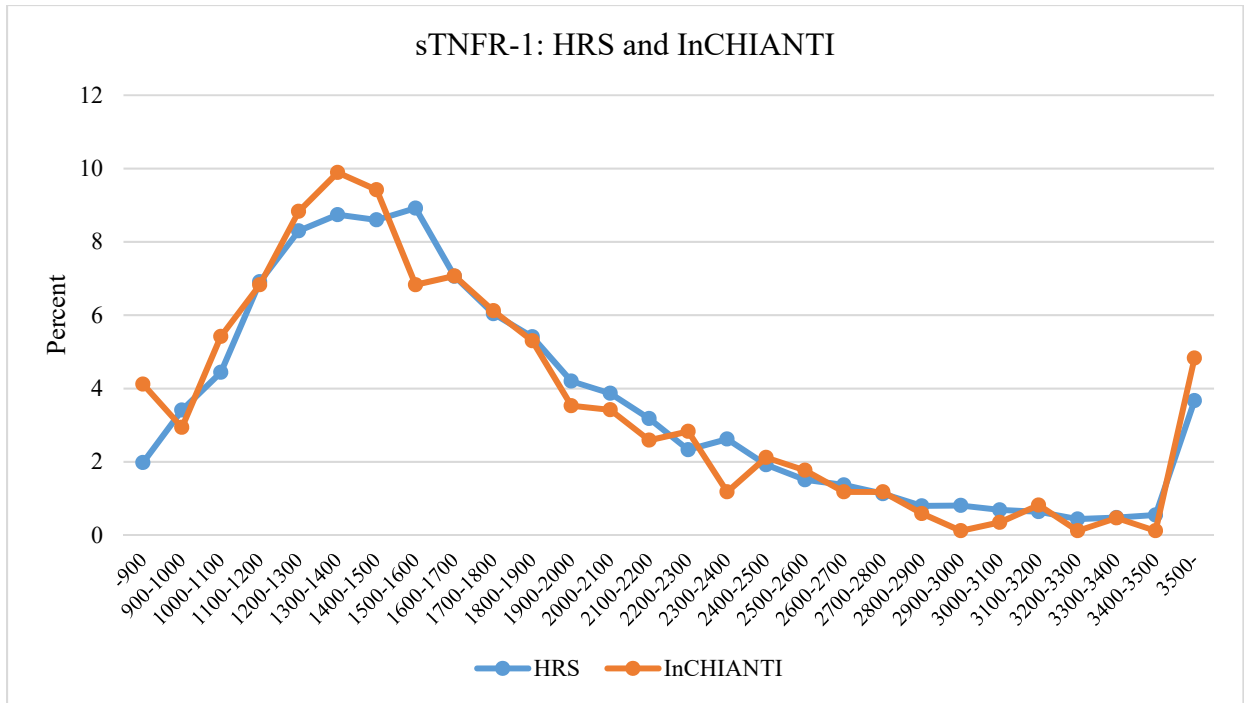


HRS: Concentration of IL-6, measured in picograms per milliliter (pg/mL)

InCHIANTI: IL-6 high-sensitivity ELISA (observed) (pg/mL) (variable name: Y\_IL6\_E)

\*Top-coded at 13.001 for >13 in InCHIANTI; same coding for HRS

data	Variable	N	Mean	Std Dev	Minimum	Maximum
HRS	IL6	9084	6.65	19.14	0.42	641.44
	IL6_topcoded	9084	4.72	3.41	0.42	13.001
InCHIANTI	IL6	849	3.49	2.82	0.58	13.001
	IL6_topcoded	849	3.49	2.82	0.55	13.001
MIDUS	IL6	663	3.29	3.28	0.31	23.00
	IL6_topcoded	663	3.14	2.60	0.31	13.001



HRS: Concentration of TNFR-1, measured in picograms per milliliter (pg/mL)

InCHIANTI: Soluble TNF-a receptor I via quantitative sandwich EIA (pg/mL) (variable name: Y\_TNFR1)

\*InCHIANTI: >6000 was coded as 7000; same coding for HRS

\*sTNFR-1 is not available in MIDUS

data	Variable	N	Mean	Std Dev	Minimum	Maximum
HRS	TNFR-1	9089	1838.07	1408.16	372.11	29734.24
	TNFR-1_topcoded	9089	1791.83	856.67	372.11	7000.00
InCHIANTI	TNFR-1	849	1755.91	866.18	654.60	7000.00
	TNFR-1_topcoded	849	1755.91	866.18	654.60	7000.00



#### D. Quality Control (QC) for 204 QC samples

We have examined 102 pairs of QC cases for cytokines. We provide the mean, SD (both within and between), reliability and CV.

#### Quality Control (QC) for 204 QC samples

	QC Pairs					
	N	Mean	Within SD (Lab)	Between SD	Reliab	CV
IL-6	204	2.24	2.36	2.36	0.9810	11.95
IL-10	204	3.05	2.03	2.03	0.9879	6.33
IL-1ra	204	453.77	269.04	269.69	0.9800	6.08
sTNFR-1	204	1307.74	447.14	447.49	0.9181	6.52
TGF- $\beta$ 1	204	52842.39	14627.04	14662.63	0.8467	8.27

## 2. VBS Vitamin D

- A. This document provides a description of the data on 3 vitamin D variables: Vitamin D2 (25-OH Vitamin D2), Vitamin D3 (25-OH Vitamin D3), and Vitamin D3 Epimer (epimer of 25-OH Vitamin D3).

**Vitamin D (Vitamin D2 and D3):** Vitamin D is measured by LC/MS/MS. The internal standard, deuterated 25-hydroxyvitamin D3, deuterated 25-hydroxyvitamin D2 are added to serum samples. The analytes are extracted and precipitated from the specimen using n-heptane. Specimens are stored in -80 freezer for 2 hours. The organic layer is removed using a gasket apparatus and dried in a speed vacuum. The reconstituted specimens are injected into the LC/MS/MS. 25-hydroxyvitamin D2 and D3 and the internal standard, deuterated 25-hydroxyvitamin D3, are eluted off a Phenomenex column with a mobile phase of 71% 2.0 mmol/L ammonium acetate, in methanol 45°C then introduced via an APCI probe to monitor the compounds of interest. System control and data acquisition are performed by the Analyst software. MultiQuant software is employed for calibration and data processing. The laboratory is enrolled in the NIST Fat Soluble Vitamins Program.

	Assay	Lower Limit of Detection	Variable Name
Vitamin D2 (ng/mL)	25-OH Vitamin D2	<0.14	pVD2
Vitamin D3 (ng/mL)	25-OH Vitamin D3	<0.82	pVD3
Vitamin D3 Epimer (ng/mL)	Epimer of 25-OH Vitamin D3	<0.94	pVD3_epimer

- B. **Descriptive Results (unweighted):** It should be noted there are a number of cases coded by the lab as “under detection” for each of these variables: 1462 for Epimer; 10 cases for D3; and 36 cases for D2.

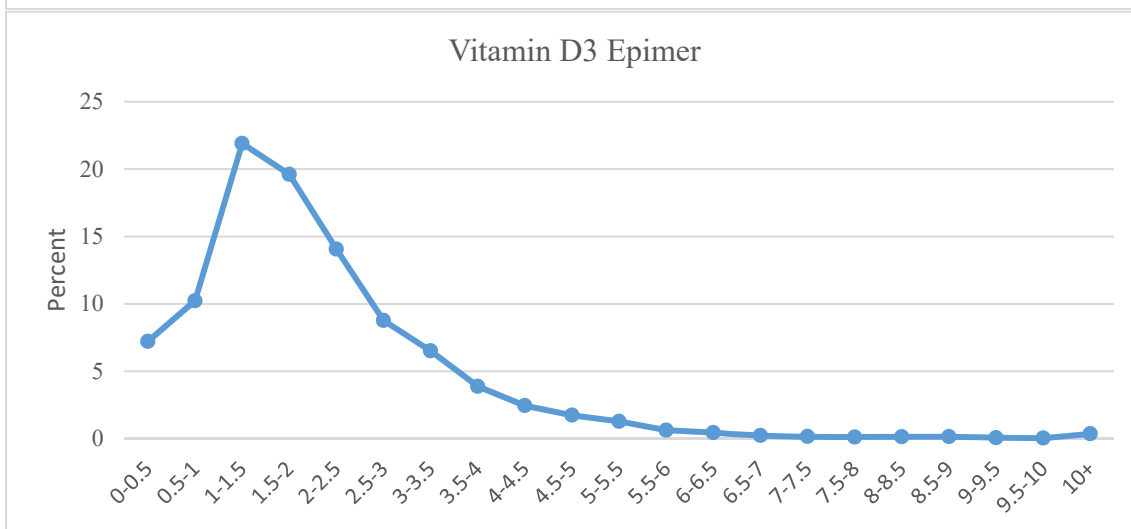
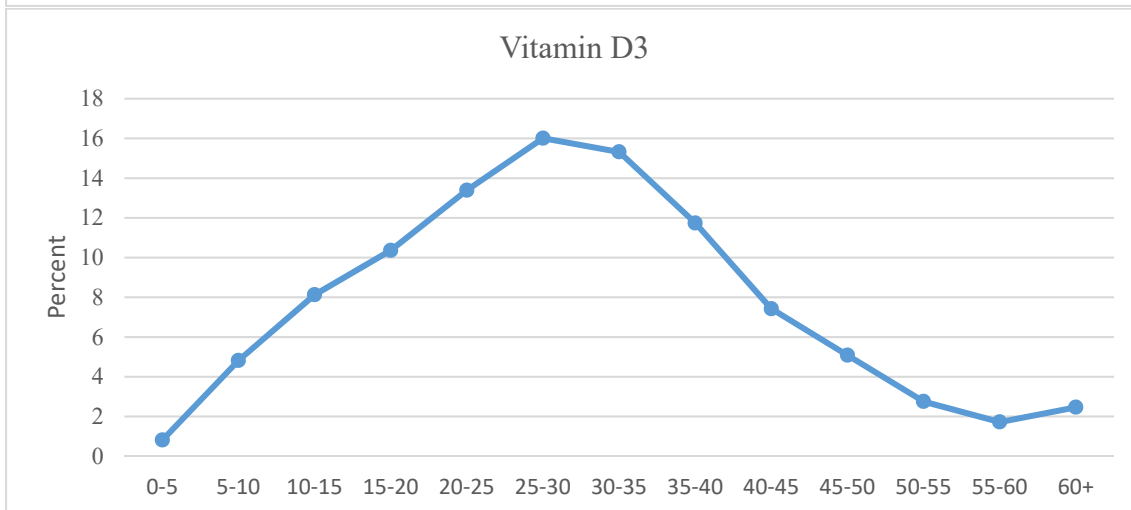
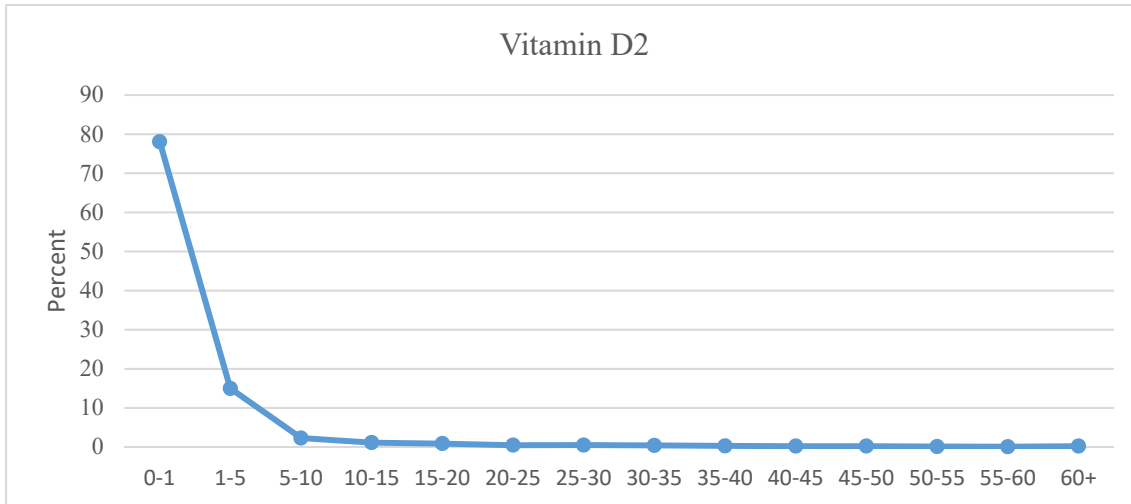
While they are coded as “under detection” in the lab data and in the data file, actual values are also provided in the data file. In our descriptive statistics below, we recoded the under detection values to a constant equal to the lower limit of detection value divided by the square root of 2, as used in National Health and Nutrition Examination Survey (NHANES).

In the Vitamin D results, 133 cases have the code of “QNS” (quantity not sufficient) and 8 cases have code “Failed Inj” (failed injection - sample was not injected into the mass spec). No values for these cases are provided in the data and they are missing in this analysis below.

### Descriptive Measures (unweighted)

	N	Mean	Std Dev	Minimum	Maximum
Vitamin D3	9770	2.12	6.66	0.03	93.33
Vitamin D2	9770	29.74	13.61	0.06	214.31
Vitamin D3_Epimer	9770	2.06	1.72	0.00	68.24

## Distributions



**C. Comparison of Vitamin D results with NHANES: (2013-2014) (weighted) Age 56+**

**NHANES 2013-2014**

25-hydroxyvitamin D2 (nmol/L)

25-hydroxyvitamin D3 (nmol/L)

epi-25-hydroxyvitamin D3 (nmol/L)

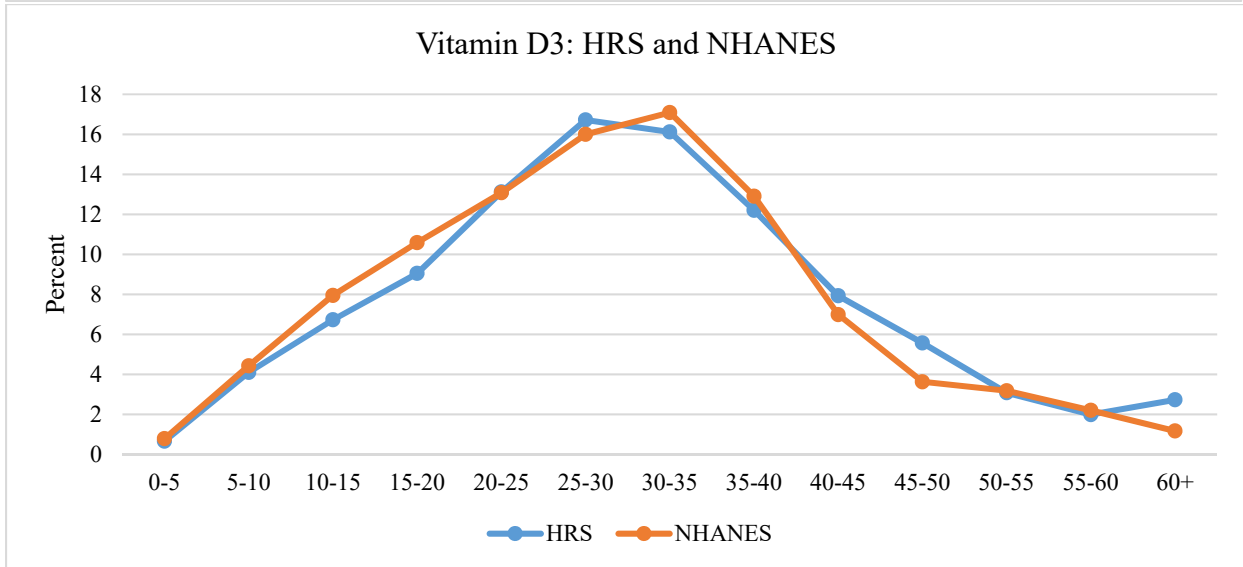
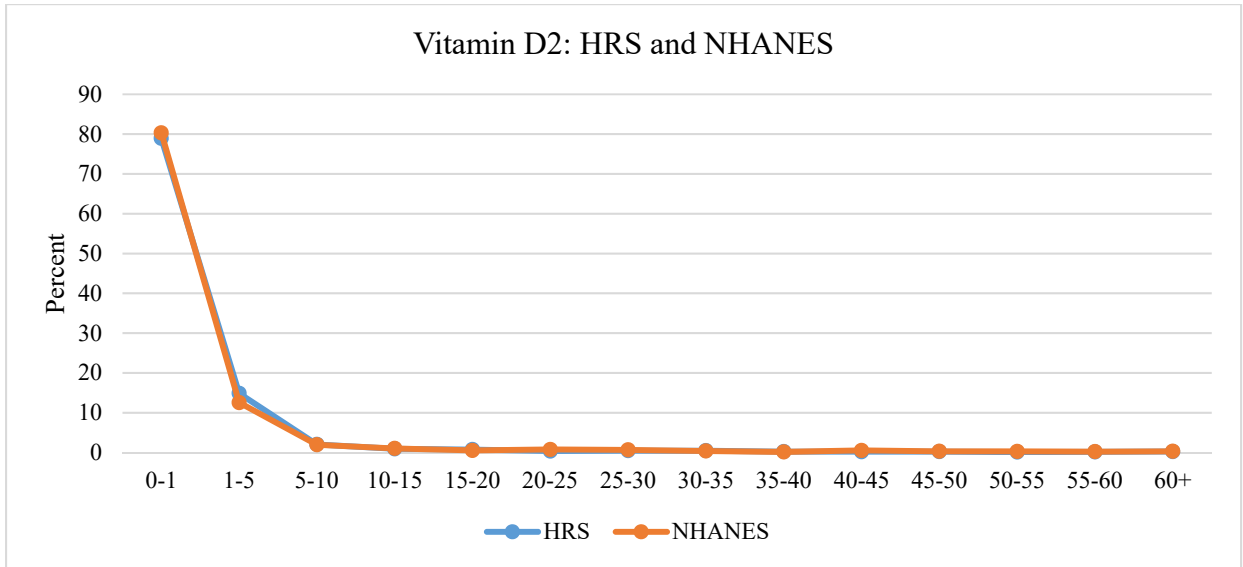
**Descriptive Results: Ages 56+ (weighted)**

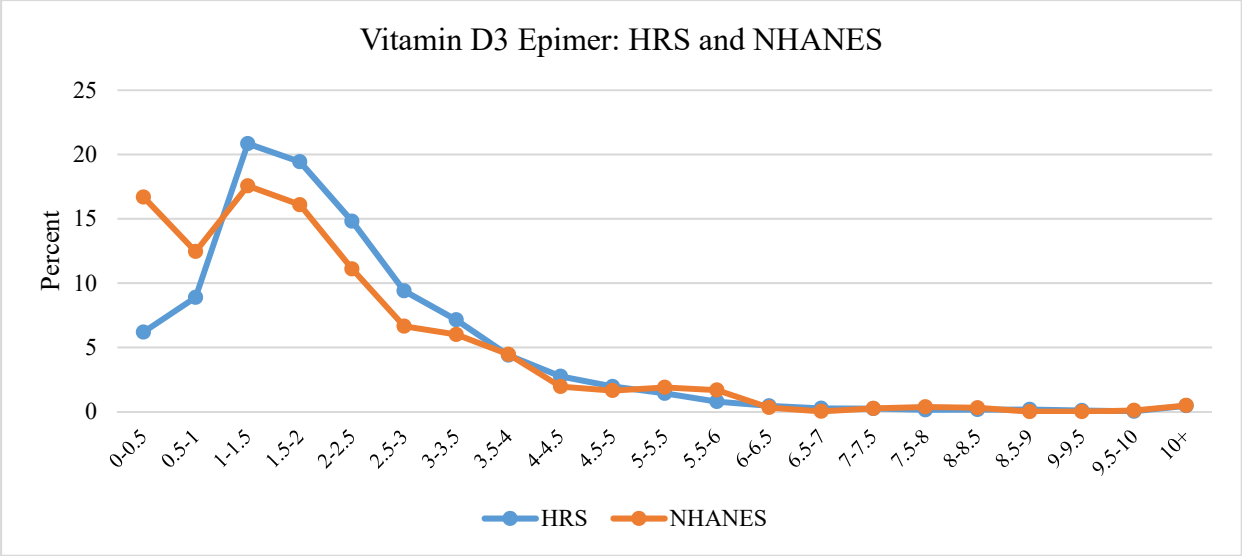
<b>Variable</b>	<b>N</b>	<b>Mean</b>	<b>Std Dev</b>	<b>Minimum</b>	<b>Maximum</b>
<b>Vitamin D2</b>					
HRS	9036	2.04	7.00	0.03	93.33
NHANES	2041	2.52	8.96	0.60	129.99
<b>Vitamin D3</b>					
HRS	9036	30.86	14.44	0.06	214.31
NHANES	2041	29.35	13.83	1.22	101.77
<b>Vitamin D3 Epimer</b>					
HRS	9036	2.18	1.91	0.00	68.24
NHANES	1993	1.98	1.76	0.46	23.96

NHANES vitamin D unit is nmol/L, converted to ng/mL here by multiplying 0.40066 for Vitamin D3 and Epimer, and 0.41266 for Vitamin D2 as suggested in the NHANES documentation:

[https://wwwn.cdc.gov/nchs/nhanes/vitamind/analyticalnote.aspx?h=/Nchs/Nhanes/2013-2014/VID\\_H.htm&t=VID\\_H%20Doc](https://wwwn.cdc.gov/nchs/nhanes/vitamind/analyticalnote.aspx?h=/Nchs/Nhanes/2013-2014/VID_H.htm&t=VID_H%20Doc)

**Distribution of Vitamin D in HRS (2016) and NHANES (2013-2014)**





**D. Vitamin D Quality Control (QC) for 204 QC samples**

We have examined 102 pairs of QC cases for Vitamin D for their mean, SD (both within and between), reliability and CV.

**Quality Control (QC) for 204 QC samples**

	QC Pairs					
	N	Mean	Within SD (Lab)	Between SD	Reliab	CV
Vitamin D2	202	1.37	2.40	2.40	0.9950	10.96
Vitamin D3	202	31.17	13.07	13.10	0.9683	5.27
Vitamin D3 Epimer	202	2.31	1.57	1.57	0.9390	15.81

### 3. VBS IGF-1 (Insulin-Like Growth Factor 1)

A. This document provides a description of the data on IGF-1.

#### **Insulin-Like Growth Factor 1 (IGF-1):**

Instrumentation: Roche COBAS 6000 chemistry analyzer (Roche Diagnostics, Indianapolis, IN)

Methodology: Manufacturer: Roche IGF-1 reagent/sandwich immunoassay method/  
electrochemiluminescence (Roche Diagnostics, Indianapolis, IN)

Precision: Interassay CV = 3.5% at 57 ng/mL and 4.4% at 334ng/mL

Limit of Detection: 7 ng/mL

FDA approved for use in the United States

	Limit of Detection	Variable Name
IGF-1 (ng/mL)	7	pIGF1

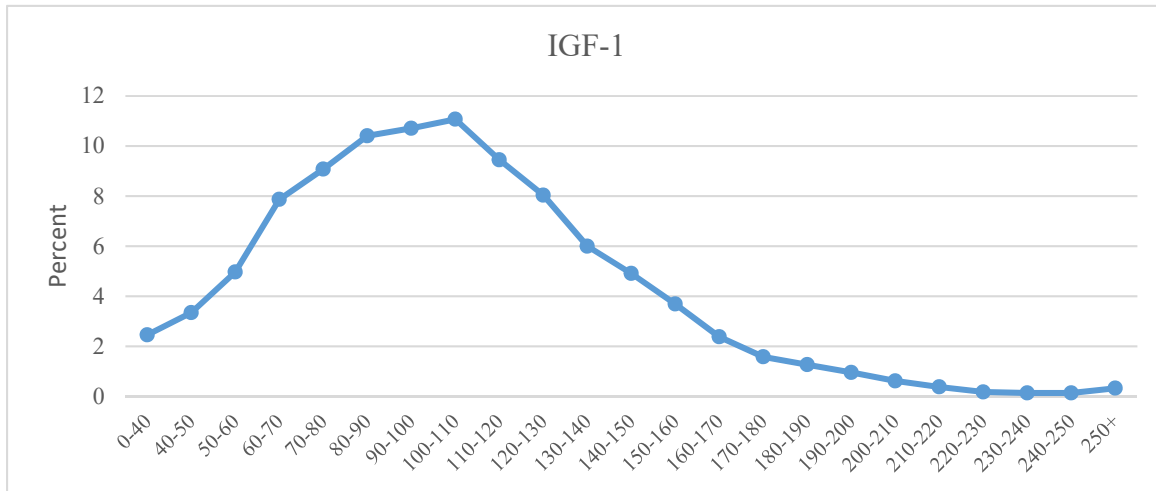
**B. Descriptive Results (unweighted):** There are four cases with values lower than detection, indicated as <7, in the original data. We recode it to 7 for this analysis. In the data, the value is shown as <7.

In the IGF-1 data, 6 cases are coded “QNS” (quantity not sufficient) and 8 cases coded “SNR” (specimen not received). No values for these cases are provided in the data. These are missing in this analysis.

#### **Descriptive Measures (unweighted)**

	<b>N</b>	<b>Mean</b>	<b>Std Dev</b>	<b>Minimum</b>	<b>Maximum</b>
<b>IGF-1</b>	9830	103.97	38.99	7.00	421.00

## Distribution



### C. Comparison of IGF-1 results with other studies: HRS 2016, MIDUS 2004-2009, and InCHIANTI 2001-2003 (Weighted)

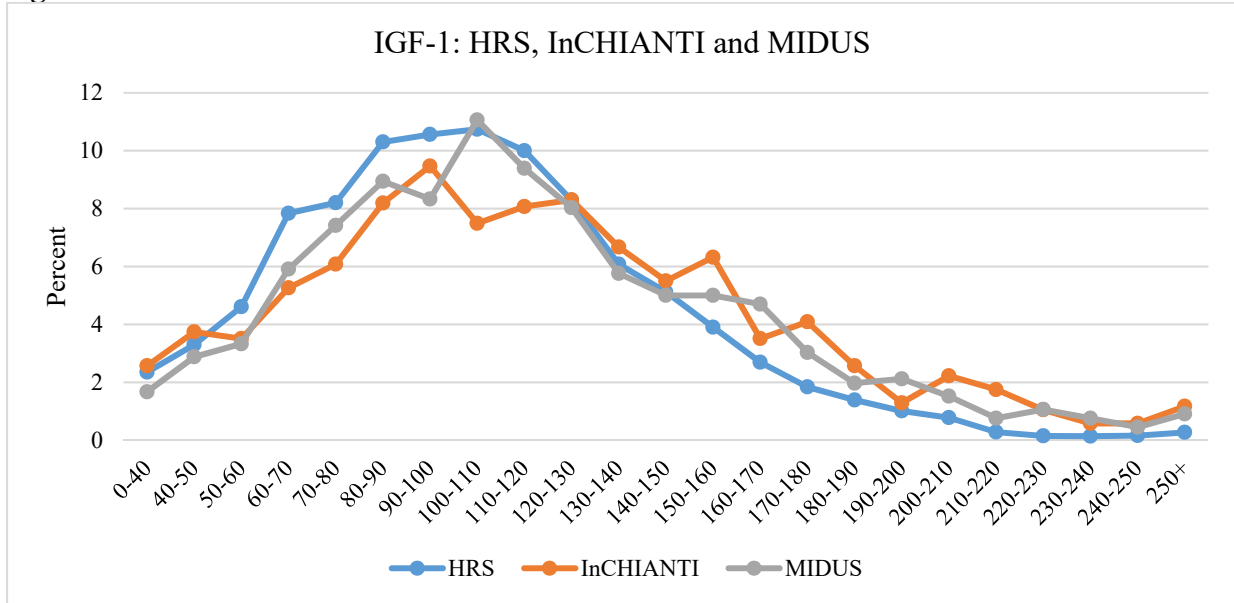
All are weighted (InCHIANTI and MIDUS weight=1): Ages 56+

#### Descriptive Results: Ages 56+ (weighted)

Data	N	Mean	Std Dev	Minimum	Maximum
<b>HRS</b>	9090	105.34	40.63	7.00	421.00
<b>InCHIANTI</b>	868	119.86	50.60	12.37	468.80
<b>MIDUS</b>	663	116.59	45.80	24.00	274.00



**Distribution of IGF-1 in HRS (2016), InCHIANTI (2001-2003) and MIDUS (2004-2009): Age 56+**



**D. Quality Control (QC) for 204 QC samples**

We have examined 102 pairs of QC cases for IGF-1 and show the mean, SD (both within and between), reliability and CV.

**Quality Control (QC) for 204 QC samples**

	QC Pairs					
	N	Mean	Within SD (Lab)	Between SD	Reliab	CV
IGF-1	204	159.16	68.20	68.37	0.9964	1.64

## **Citing this Document**

Please include the following citation in any research reports, papers, or publications based on these data:

**In text:** "The HRS (Health and Retirement Study) is sponsored by the National Institute on Aging (NIA U01AG009740) and is conducted by the University of Michigan."

**In references:** "Crimmins E, Faul J, Kim J, Thyagarajan B, Weir D. Cytokines, Vitamin D, and IGF 1 from the 2016 Venous Blood Study: 2016 Health and Retirement Study. Ann Arbor, MI: Survey Research Center, Institute for Social Research, University of Michigan; 2020."