Methodology Session: Add Health Wave IV Biomarker Data

Eric A. Whitsel
Carolina Population Center
University of North Carolina at Chapel Hill

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Add Health

- National Longitudinal Study of Adolescent to Adult Health
  - nationally representative
    - region, pop density, school size / type & ethnicity
  - school-based sample of students in grades 7-12, n=20,745
    - 80 high schools
    - 52 middle schools
  - longitudinal
    - Wave I (‘94-’95): in-school & in-home (79%)
    - Wave II (‘96): in-home (88%)
    - Wave III (‘01-’02): in home (77%)
    - Wave IV (‘07-’09): in-home, n=15,701 (80%)
  - focused on social, behavioral & biological linkages across the life course

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Wave IV Biomarkers – Overview

- Types
- Measures & Classification
- Collection
- Central Labs
- Challenges
- Findings
- Resources
- Discussion

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Wave IV Biomarkers – Types

- Cardiovascular
- Anthropometric
- Metabolic
- Inflammatory
- Immune
- Genetic
- Pharmacologic

Biomarkers: Add Health Wave IV*
Cardiovascular
SBP [mmHg]
DBP [mmHg]
PR [beats/min]
Anthropometric
Weight [kg]
Height [cm]
Waist Circumference [cm]
Metabolic
Hb_{A1c} [%]
Glucose [mg/dl]
TC [mg/dL]
HDL-C [mg/dL]
TG [mg/dL]
Inflammatory / Immune
$_{hs}$CRP [mg/L]
EBV (AU/ml)
Genetic
Candidate Gene Loci + AIMs + 10^6 SNPs
Pharmacologic
Medication Use / Classification

*BMI [kg/m^2], PP [mmHg], MAP [mmHg], LDL-C [mg/dL], TC:HDL-C, non-HDL-C [mg/dL] are derived from the above using conventional formulae.

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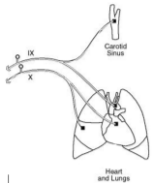
Wave IV Biomarkers – Measures

- Cardiovascular
  - Primary
    - systolic blood pressure (SBP)
    - diastolic blood pressure (DBP)
    - pulse rate (PR)
  - Secondary
    - pulse pressure (PP = SBP - DBP)
    - mean arterial pressure (MAP = [SBP + 2 × DBP] ÷ 3)
    - baroreflex sensitivity (BRS)
    - pulse rate recovery (PRR)
    - systolic blood pressure recovery (SBPR)



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Wave IV Biomarkers – Measures

- Cardiovascular
  - SBP/DBP classified according to JNC 7 guidelines*
    - < 120/80 mm Hg — Normal
    - 120-139/80-89 mm Hg — Pre-Hypertension
    - 140-159/90-99 mm Hg — Stage 1 Hypertension
    - ≥ 160/100 mm Hg — Stage 2 Hypertension

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*The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7). Hypertension 2003;42:1206.

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Wave IV Biomarkers – Measures

- Anthropometric
  - Primary
    - weight
    - height
    - waist circumference (waist)
  - Secondary
    - body mass index (BMI = weight in kg / height in m^2)

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Wave IV Biomarkers – Measures

- Anthropometric
  - Classified according to NHLBI Evidence Report*
    - BMI
      - < 18.5 kg/m^2 Underweight
      - 18.5-24.9 kg/m^2 Normal
      - 25.0-25.9 kg/m^2 Overweight
      - 30.0-34.9 kg/m^2 Obesity, Stage I
      - 35.0-39.9 kg/m^2 Obesity, Stage II
      - ≥ 40.0 kg/m^2 Obesity, Stage III
    - Waist
      - ≤ 88 (102) cm in ♀ (♂) Lower Risk
      - > 88 (102) cm in ♀ (♂) High Risk

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*Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults – the evidence report. Obesity Res 1998;6(S2);51S-210S.

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Wave IV Biomarkers – Measures

- Metabolic, lipids*
  - Primary
    - total cholesterol (TC)
    - high density lipoprotein cholesterol (HDL-C)
    - triglycerides (TG)
  - Secondary
    - low density lipoprotein cholesterol (LDL-C = TC - HDL-C - TG ÷ 5)†
    - TC:HDL-C ratio (TC:HDL-C = TC / HDL-C)
    - non-HDL-C (= TC - HDL-C)

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*Random. †The Friedwald (1972) equation applies when TG < 400.

Wave IV Biomarkers – Measures

- Metabolic, lipids*
  - Classified according to NCEP ATP III guidelines†

• TC (mg/dl)	< 200	desirable
	200-239	borderline high
	≥ 240	high
• HDL-C (mg/dl)	< 40	low
	≥ 60	high
• LDL-C (mg/dl)	< 100	optimal
	100-129	near optimal
	130-159	borderline high
	160-189	high
	≥ 190	very high
• TG‡ (mg/dl)	< 150	normal
	150-199	borderline high
	200-499	high
	≥ 500	very high

  - Ranked by decile

*Random. †Third Report of the National Cholesterol Education Program (NCEP) on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). ‡Spuriously high in the non-fasting state.

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Wave IV Biomarkers – Measures

- Metabolic, glucose homeostasis*
  - Primary
    - glycosylated hemoglobin (HbA_{1c})
    - glucose
  - Secondary
    - mean plasma glucose ($MPG = 35.6 \times HbA_{1c} - 77.3$)†
    - estimated average glucose ($EAG = 28.7 \times HbA_{1c} - 46.7$)‡

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*Random. †Rohlfing et al. Diabetes Care 2002;25(2):275-278. ‡Nathan et al. Diabetes Care 2008;31(8):1-6.

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Wave IV Biomarkers – Measures

- Metabolic, glucose homeostasis*
  - Classified according to ADA guidelines†
    - fasting glucose

≤ 99 mg/dl	normal
100-125 mg/dl	impaired
≥ 126 mg/dl	diabetes

    - random glucose

≥ 200 mg/dl	diabetes

    - HbA_{1c}

5.7-6.4%	increased risk for diabetes
≥ 6.5%	diabetes

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*Random. †American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diab Care 2013;36(S1):S67-S74.

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Wave IV Biomarkers – Measures

- Immune / Inflammatory
  - Epstein-Barr viral capsid antigen IgG (EBV)
  - high sensitivity C-reactive protein (hsCRP)
    - classified according to CDC / AHA guidelines*
      - low < 1 mg/L
      - average 1-3 mg/L
      - high > 3 mg/L
    - knowing that values > 10 mg/L must trigger searches for factors capable of confounding hsCRP-based CVD risk estimates

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*Pearson et al. Markers of inflammation and cardiovascular disease. Application to clinical and public health practice. A statement for healthcare professionals from the CDC and AHA. Circulation 2003;107:499-511.

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Wave IV Biomarkers – Measures

- Genetic
  - candidate gene loci & SNP panels } focusing on DA, 5-HT & NA neurotransmission systems with known roles in behavior and health
  - ancestry informative markers (AIMs)
  - 10^6 SNPs
- Pharmacologic
  - prescription medications
  - select over-the-counter medications (salicylates & NSAIDS)
  - automatically spelled
  - therapeutically classified (Multum Lexicon Plus®)
    - example HYDROCHLOROTHIAZIDE (THIAZIDE DIURETIC)

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Wave IV Biomarkers – Measures

- Antihypertensives

```
data drug;
   array s {4} set1-set4;
   do i=1 to 4;
      if substr(s{i},1,7) =  '040-047'                                then bb =1;   /***beta-blockers                                          ***/
      if s{i}             =  '040-049-156'                            then di =1;   /***thiazide diuretics                                   ***/
      if substr(s{i},1,7) =  '040-042'                                then ai =1;   /***angiotensin converting-enzyme inhibitors             ***/
      if substr(s{i},1,7) in('040-043','040-044')                     then aa =1;   /***antiadrenergics                                     ***/
      if substr(s{i},1,7) =  '040-048'                                then ccb=1;   /***calcium channel blocker                            ***/
      if substr(s{i},1,7) =  '040-053'                                then vd =1;   /***vasodilators                                       ***/
      if substr(s{i},1,7) =  '040-056'                                then at2=1;   /***angiotensin II receptor blockers                    ***/
      if substr(s{i},1,7) in('040-055')                               then ca =1;   /***combination antihypertensives                      ***/
      if bb=1 or di=1 or ai=1 or aa=1 or ccb=1 or vd=1 or at2=1 or ca=1 then ah =1;   /***any antihypertensive                                  ***/
   end;
run;
```

- Antihyperlipidemics

```
data drug2;
   array s {4} set1-set4;
   do i=1 to 4;
      if substr(s{i},1,7) = '019-173'                                 then st=1;    /***HMG-CoA reductase inhibitors                         ***/
      if substr(s{i},1,7) = '019-174'                                 then mi=1;    /***miscellaneous antihyperlipidemic agents              ***/
      if substr(s{i},1,7) = '019-241'                                 then fi=1;    /***fibric acid derivatives                              ***/
      if substr(s{i},1,7) = '019-252'                                 then bi=1;    /***bile acid sequestrants                               ***/
      if substr(s{i},1,7) = '019-316'                                 then ab=1;    /***cholesterol absorption inhibitors                    ***/
      if substr(s{i},1,7) = '019-317'                                 then co=1;    /***antihyperlipidemic combinations                      ***/
      if st=1 or mi=1 or fi=1 or bi=1 or ab=1 or co=1                 then al=1;    /***any antihyperlipidemic                               ***/
   end;
run;
```

- Antidepressants

```
data drug3;
   array s {4} set1-set4;
   do i=1 to 4;
      if s{i}             ='242-251-079'                              then co =1;  /***psychotherapeutic combinations:  antipsychotic + ssri or tca***/
      if s{i}             ='242-249-076'                              then mi =1;  /***miscellaneous antidepressants:  st. john's wort          ***/
      if s{i}             ='242-249-208'                              then ssr=1;  /***selective serotonin reuptake inhibitors                 ***/
      if s{i}             ='242-249-209'                              then tr =1;  /***tricyclic antidepressants                            ***/
      if s{i}             ='242-249-250'                              then ma =1;  /***monoamine oxidase inhibitors                           ***/
      if s{i}             ='242-249-306'                              then ph =1;  /***phenylpiperazine antidepressants                       ***/
      if s{i}             ='242-249-307'                              then te =1;  /***tetracyclic antidepressants                          ***/
      if s{i}             ='242-249-308'                              then ssn=1;  /***selective serotonin norepinephrine reuptake inhibitors  ***/
      if co=1 or mi=1 or ssr=1 or tr=1 or ma=1 or ph=1 or te=1 or ssn=1 then ad =1;  /***any antidepressant                                    ***/
end;
run;
```

- And other classes

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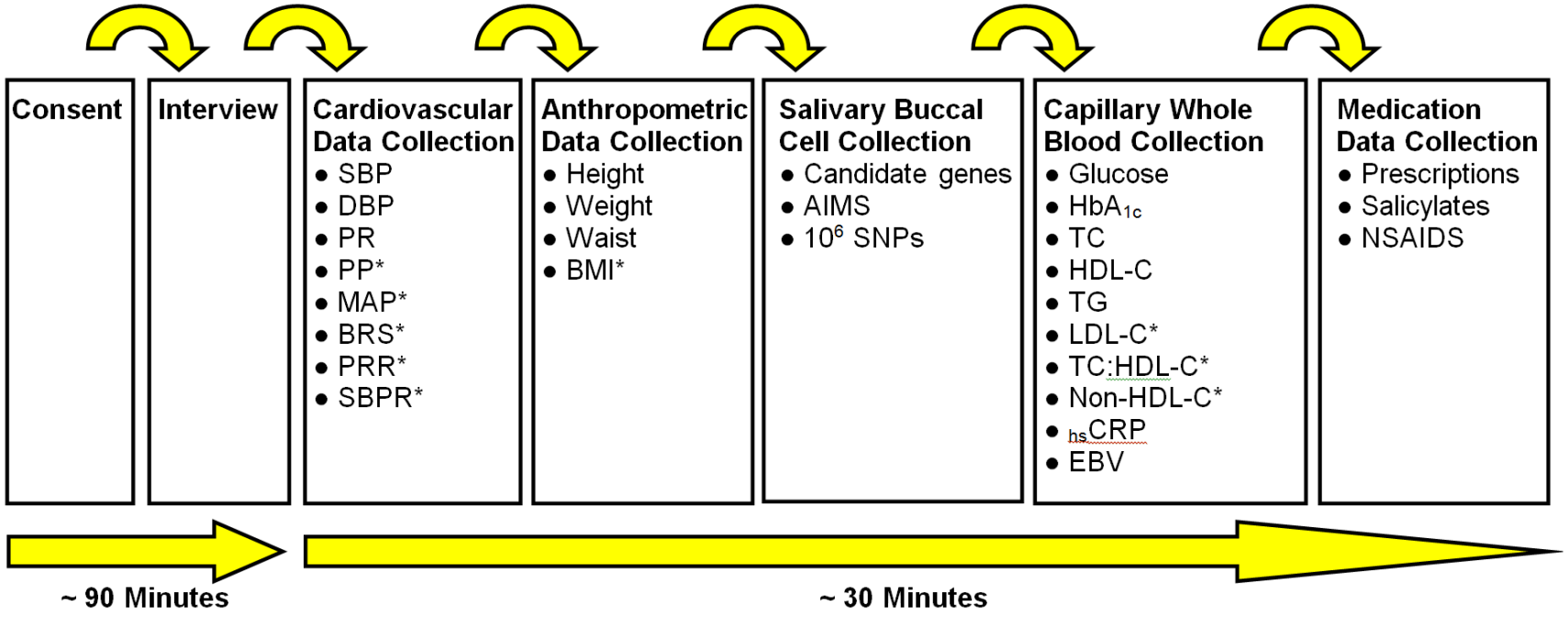
Wave IV Biomarkers – Collection Sequence



*Secondary

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Wave IV Biomarkers – Collection Methods

- Cardiovascular Data Collection Equipment

Measures	Equipment	Picture	Specifications
SBP	MicroLife		30-280/40-200 BP/PR range
DBP	3MC1-PC_IB		1-unit graduations
PR	Oscillometric		198 measure recall
PP*	BP		± 3 mmHg accuracy
MAP*	Monitor		± 5 beat pulse accuracy
			BHS-approved
			4 "AA" battery-powered
			w/ AC adapter + USB cable
			2 cuffs (24-41 cm)
			160 x 140 x 98 mm
			735 g (w/ batteries)
			< $65

*Secondary

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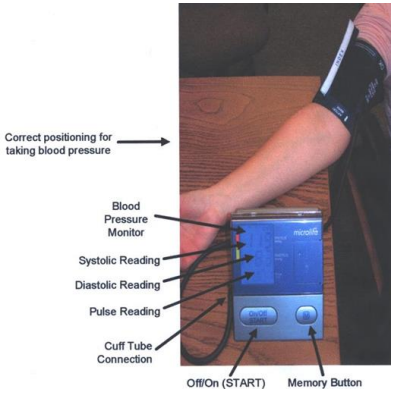
Wave IV Biomarkers – Collection Methods

- Cardiovascular Data Collection Protocol
  - trained & certified staff
  - resting & seated respondents
  - cuff matched to arm circumference
  - SBP, DBP & PR
    - measure 3X
    - @ 30-sec intervals
    - double enter
    - automatically average over last 2



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The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7). Hypertension 2003;42:1206.

Wave IV Biomarkers – Collection Methods

- BRS, PRR & SBPR Estimation Protocol
  - restrict to participants with
    - all 3 measures of SBP (mm Hg) & PR (beats/min)
    - non-missing sampling weights
  - convert PR to its unit-corrected reciprocal
    - RR (ms) = 60,000 ÷ PR
  - run weighted, random-effects models
    - $Y_{ij} = \beta_0 + \beta_1 X_{ij} + u_{0j} + u_{1j} X_{ij} + e_{0ij}$, where for e.g.
    - BRS: (Y_{ij}, X_{ij}) = *i*th (RR, SBP) *on j*th *participant*
  - estimate participant-specific slopes
    - $\sum(fixed + random\ slopes) = \beta_1 + u_{1j}$

Example of estimating SBPR

AID	β_1	μ_{ij}	SBPR
1	-1.1	-3.6	-4.7
2	-1.1	-0.7	-1.8
3	-1.1	0.3	-0.8
4	-1.1	1.8	0.7
5	-1.1	-1.2	-2.3

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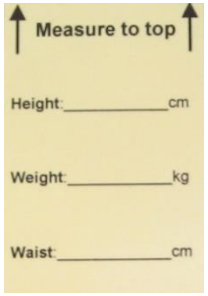
Wave IV Biomarkers – Collection Methods

- Anthropometric Data Collection Equipment

Measure	Equipment	Pictures	Specifications
Height	**Carpenter's Square**		**portable light weight inexpensive true 90° angle**
	Tape Measure		**10 ft steel tape**
	Post-it Notes		**adherent pre-labeled**

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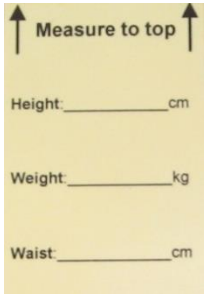
Wave IV Biomarkers – Collection Methods

- Anthropometric Data Collection Equipment

Measure	Equipment	Pictures	Specifications
Weight	**Health-O-Meter 844KL High Capacity Digital Scale**	 	**4-point load cell** **digital display in lb / kg** **440 lb maximum** **0.1 lb graduations** **long life Li^{++} battery** **low battery warning** **1-year warranty** **12.6 x 12.6 in** **4.5 lb** **< $70**

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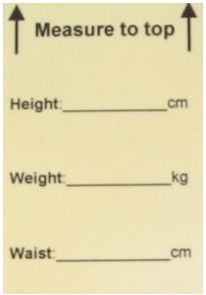
Wave IV Biomarkers – Collection Methods

- Anthropometric Data Collection Equipment

Measure	Equipment	Pictures	Specifications
Waist	Seca 200 Circumference Tape Measure	 	200 cm maximum 2-sided cm scaling 1 mm graduations fiberglass tape plastic case automatic roll-up end-peg positioner 90 x 25 x 65 mm 50 g < $13

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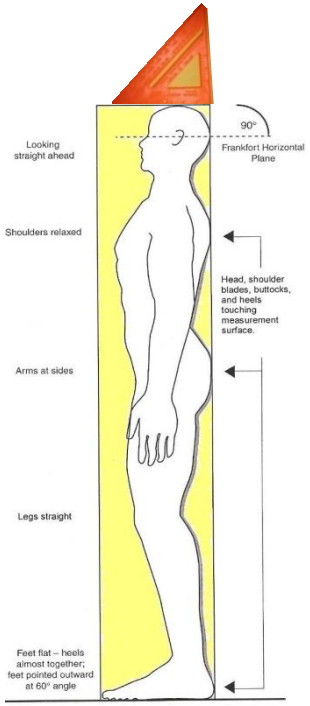
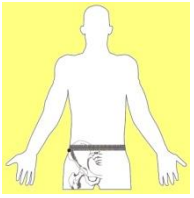
Wave IV Biomarkers – Collection Methods

- Anthropometric Data Collection Protocol
  - trained & certified staff
  - dressed & unshoed respondents
  - standing on uncarpeted floor
  - measure
    - height to nearest 0.5 cm
    - weight to nearest 0.1 kg
    - waist to nearest 0.5 cm
      - @ superior border of iliac crest
      - @ end expiration
      - horizontal to floor
    - hair/shoe height to nearest 0.5 cm, as needed





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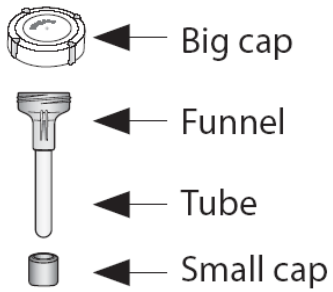
Wave IV Biomarkers – Collection Methods

- Salivary Buccal Cell DNA Collection Equipment

Measures	Equipment	Schematic	Specifications
Genes **SNP panels** **AIM**	**DNAGenotek** **Oragene•DNA** **Collection** **Kit**		**collection funnel** **preservative-containing cap** **tube for storage** **small cap for shipping**

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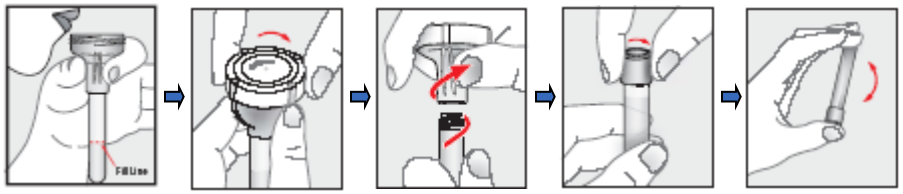
Wave IV Biomarkers – Collection Methods

- Salivary Buccal Cell DNA Collection Protocol
  - trained & certified staff
  - respondents spit into funnel
  - remove funnel
  - turn big cap clockwise to add preservative
  - turn big cap counter-clockwise to remove it
  - replace big cap with small cap
  - invert 5X to mix saliva and preservative
  - package & FedEx to lab



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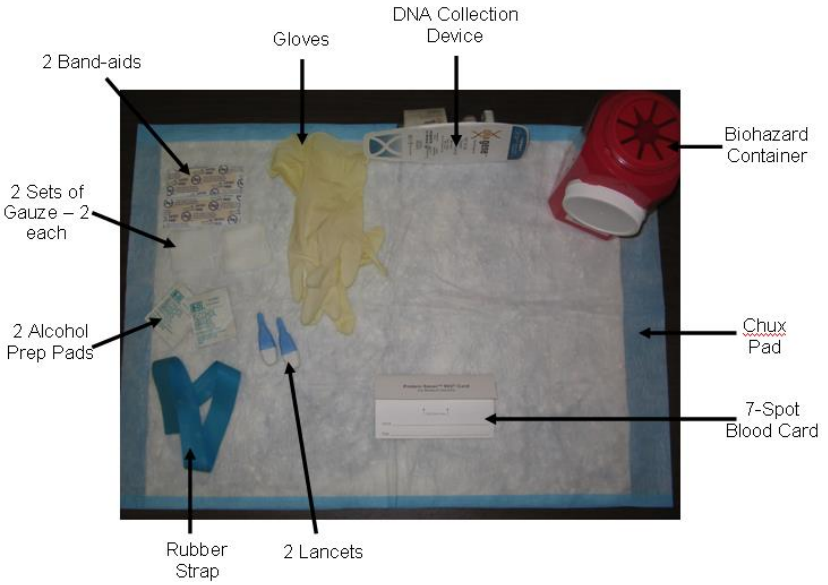
Wave IV Biomarkers – Collection Methods

- Dried Whole Blood Spot Collection Equipment

Measures	Equipment
TC	Gloves
HDL-C	Band-Aids
TG	Gauze
HbA_{1c}	Alcohol prep pads
LDL-C*	Tourniquet
TC:HDL-C*	Lancets
Non-HDL-C*	7-spot cards
Glucose*	Chux pad
hsCRP	Biohazard container
EBV	

Workstation



*Secondary

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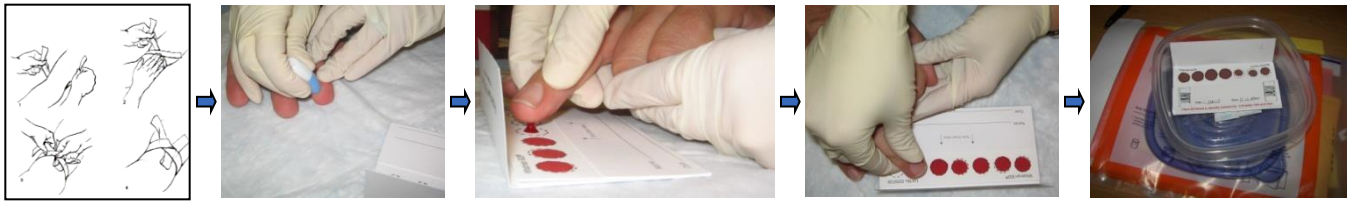
Wave IV Biomarkers – Collection Methods

- Dried Whole Blood Spot Collection Protocol
  - trained & certified staff
  - non-fasting respondents
  - clean middle or ring finger w/ alcohol prep pad
  - apply tourniquet to arm
  - prick finger & firmly wipe away 1st drop
  - drop up to 7 blood spots onto card
  - repeat prick X1, if necessary
  - air dry over desiccant
  - package & FedEx to lab



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Wave IV Biomarkers – Central Labs

- Salivary Buccal Cell DNA
  - **Andy Smolen, Ph.D. (PI)**
    Director, Genotyping Laboratory
    Institute for Behavioral Genetics
    University of Colorado (Boulder, CO)
- Dried Whole Blood Spots
  - **Mark H. Wener, M.D. (PI)**
    Director, UW Medical Center Laboratories
    Department of Laboratory Medicine
    University of Washington (Seattle, WA)
  - **Robert Ray, Ph.D.**
    Director, FlexSite Diagnostics, Inc. (Palm City, FL)

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Wave IV Biomarkers – Challenges

- Scope
- Reliability
- Digit Preference
- Trend / Cyclicity
- Comparability
- Validity

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Wave IV Biomarkers – Challenges

- Scope
  - Took steps to prepare for it
    - automated handling & tracking
    - scaled staffing & stocking procedures
    - industrialized processes
    - planned for unanticipated shortfalls
  - Monitored participant, sample & data flow

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Scope

Map
Illustrating
Geographic
Distribution of
Participants

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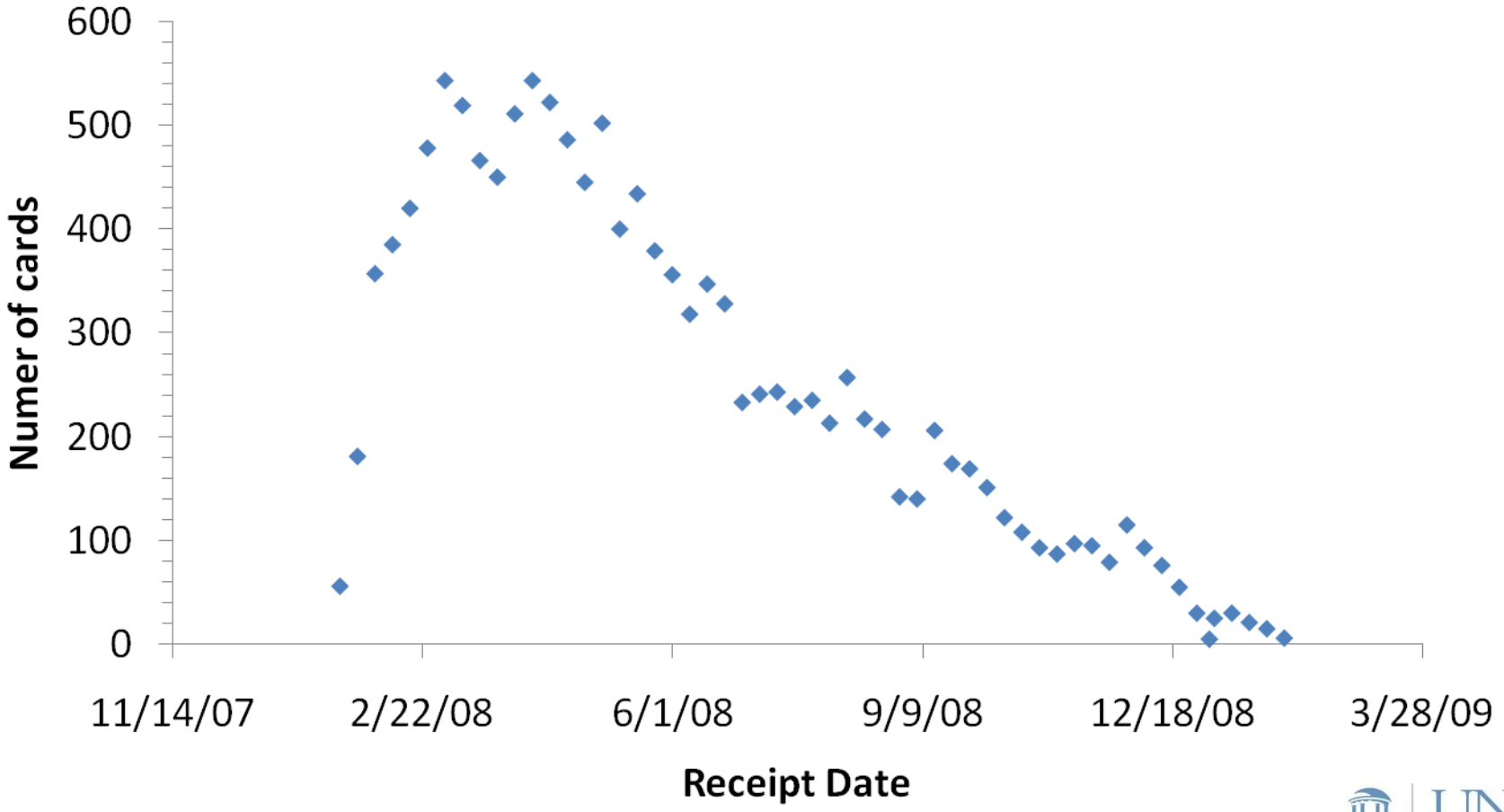
Scope



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Scope

Scope

AYDROCHLOROTHIAZIDE	HYDROCHLORAZIDE	HYDROCHLORTHIACIDE
CHYDROCHLOROTHIAZIDE	HYDROCHLORHTIAZIDE	HYDROCHLORTHIAZ
HCT	HYDROCHLORIAZ	HYDROCHLORTHIAZIDE
HCTC	HYDROCHLORIDE	HYDROCHLORTHIAZINE
HCTL	HYDROCHLORITHIAZIDE	HYDROCHLORTHIZIDE
HCTS	HYDROCHLORIZIDE	HYDROCHLOTHIAZIDE
HCTX	HYDROCHLORO THIAZIDE	HYDROCHLOTHIZ
HCTZ	HYDROCHLOROPHIADIZE	HYDROCHLOTOTHIZIDE
HCYZ	HYDROCHLOROT	HYDROCHLTHIAZ
HLTZ	HYDROCHLOROTHAZIDE	HYDROCHLTHIAZIDE
HTCZ	HYDROCHLOROTHIAZ	HYDROCHLTHIZ
HTZ	HYDROCHLOROTHIAZI	HYDROCHOLORATHIAZIDE
HYDORCHLORO THIAZIDE	HYDROCHLOROTHIAZID	HYDROCHOLOROTHIAZIDE
HYDRACHLORAZIDE	**HYDROCHLOROTHIAZIDE**	HYDROCHOLOROTHIZIDE
HYDRECHLOROTHIAZIDE	HYDROCHLOROTHIZ	HYDROCHOLORTHIAZIDE
HYDRO CLOROTHIAZIDE	HYDROCHLOROTHIZIDE	HYDROCHOLOTHIAZIDE
HYDRO CLORTHIAZIDE	HYDROCHLOROTHLIAZIDE	HYDROCHOROTHIAZIDE
HYDROCALOROTHIAZIDE	HYDROCHLOROTHUAZIDE	HYDROCHOROTHIZIDE
HYDROCHL THIAZ	HYDROCHLOROTHYAZIDE	HYDROCLOROTHIAZIDE
HYDROCHLITHIAZ	HYDROCHLOROTMIAZIDE	HYDROTHIAZIDE
HYDROCHLORATHIAZIDE	HYDROCHLOROZIDE	HZTC
HYDROCHLORATHIZE	HYDROCHLORTHAIZIDE	MCHT

Wave IV Biomarkers – Challenges

- Reliability
  - Took steps to increase it
    - (fixed setting)
    - standardized protocols
    - calibrated, tested equipment
    - used same source & type of supplies, reagents, assays
    - uniformly trained & certified staff
    - automated data collection
    - automated range checks
    - duplicated data entry
    - conducted post-encounter participant interviews
  - Monitored it
    - conducted intra-individual variation (IIV) studies

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Reliability

- IIV Study Protocol (2007 - 2009)
  - computed n needed to estimate the reliability assuming
    - measures are interval-scale
    - reliability estimated as an ICC
    - underlying ICC = 0.7 & precise, 95%CI = 0.2
  - identified a race/ethnicity- & gender-stratified random sample
    - ~ 50 participants in Pre-Test & ~ 50 in Main Study
  - excluded siblings and pregnant women
  - examined participants 2x, 1-2 wk apart
    - visit 1: full interview + biomarkers
    - visit 2: abbreviated interview + biomarkers
  - masked labs & technicians to participant identity
  - processed the biomarkers

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Reliability

Characteristics of the IIV population*

Characteristic		Mean (sd) or n (%) Visit 1	Visit 2
Age (y)		28.5 (1.9)	
Female		50 (50%)	
Race/Ethnicity	Non-Hispanic White	64 (64%)	
	Non-Hispanic Black	16 (16%)	
	Hispanic	12 (12%)	
	Other	8 (8%)	
Pre-Test Participant		42 (42%)	
Fasting duration (hr)		4.8 (4.9)	6.5 (6.7)
Fasting ≥ 8 hr		17 (17%)	30 (30%)
Fasting ≥ 9 hr		14 (14%)	28 (28%)
V1-V2 Interval (d)		8.6 (3.0)	
Same Field Interviewer Both Visits		84 (84%)	

*Based on a final sample of 100 IIV participants.

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Reliability

- IIV Analysis Method
  - Nested, random-effects model partitioning biomarker variance into its components:
  - $Y_{ijk} = \mu + P_i + V_j(P_i) + \varepsilon_{ijk}$
  - where:
    - Y_{ijk} = value @ jth visit of ith participant
    - μ = intercept
    - P_i = ith participant
    - $V_j(P_i)$ = jth visit nested within ith participant
    - ε_{ijk} = random error
  - assuming:
    - P_i, $V_j(P_i)$ and ε_{ijk} are independent and ~ $N(0, \sigma^2)$
  - under this assumption:
    - $\sigma^2_T = \sigma^2_{BP} + \sigma^2_{BV} + \sigma^2_{WV}$ and ICC = $\sigma^2_{BP} / \sigma^2_T$
    - MDC = $2.77 * \sqrt{\sigma^2{}_{BV} + \sigma^2{}_{WV}}$
    - MDD = $\sqrt{2 * \frac{\sigma^2{}_T}{n}} * (t_{\propto(df)} + t_{\beta(df)})$ where $df = 2 * n - 2$

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Reliability

Reliability of Biomarkers: Add Health, Wave IV (2007-2009)

Type	Measure	ICC (95% CI)
Anthropometric	Weight	1.00 (1.00-1.00)
	Height	0.98 (0.98-0.99)
	BMI	0.99 (0.99-1.00)
	Waist	0.98 (0.97-0.99)
Cardiovascular	BRS	0.84-0.94*
	PRR	0.85-0.86*
	SBP	0.81 (0.74-0.88)
	SBPR	0.76-0.79*
	DBP	0.68 (0.57-0.79)
	PR	0.47 (0.31-0.63)
Metabolic	HbA_{1C}	0.97 (0.96-0.98)
	TG	0.71 (0.60-0.81)
	TC	0.40 (0.22-0.58)
	Glucose	0.40 (0.22-0.59)
	HDL-C	0.39 (0.21-0.57)
Inflammatory	$_{hs}CRP$	0.70 (0.59-0.81)
Immune	EBV	0.97 (0.96-0.98)

ICC (95% CI) = intra-class correlation coefficient, 95% confidence interval. *Tabulated values for BRS are ranges of variance partitioning coefficients over SBPs of 90-180 mm Hg, and for PRR and SBPR, over time.

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Reliability

Reliability of Biomarkers Add Health, Wave IV (2007-2009)

Type	Measure	ICC (95% CI)	MDC	MDD	Unit
Anthropometric	Weight	1.00 (1.00-1.00)	2.8	3.9	kg
	Height	0.98 (0.98-0.99)	3.8	1.7	cm
	BMI	0.99 (0.99-1.00)	1.6	1.3	kg/m^2
	Waist	0.98 (0.97-0.99)	7.7	2.9	cm
Cardiovascular	SBP	0.81 (0.74-0.88)	14	2.0	mm Hg
	DBP	0.68 (0.57-0.79)	15	1.6	mm Hg
Metabolic	HbA_{1C}	0.97 (0.96-0.98)	0.4	0.1	%
	TG	0.71 (0.60-0.81)	55	4.1	mg/dl
	TC	0.40 (0.22-0.58)	158	17	mg/dl
	Glucose	0.40 (0.22-0.59)	139	11	mg/dl
	HDL-C	0.39 (0.21-0.57)	36	2.7	mg/dl
Inflammatory	$_{hs}CRP$	0.70 (0.59-0.81)	2.1	0.2	mg/L
Immune	EBV	0.97 (0.96-0.98)	47	17	AU/ml

ICC (95% CI) = intra-class correlation coefficient, 95% confidence interval. MDC = minimal detectable change with 95% confidence (one sample; repeated measures). MDD = minimal detectable difference with 95% confidence and a 5% type II error rate (two samples, each of n=1000).

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Reliability

- IIV Study Results
  - anthropometric measures
    - excellent, near unity
  - cardiovascular measures
    - BRS excellent
    - PRR, SBP, SBPR & DBP acceptable, typical
    - PR marginal, typical
  - metabolic measures
    - HbA_{1c} excellent, near unity
    - TG acceptable
    - TC, glucose & HDL-C marginal
  - immune / inflammatory measures
    - EBV excellent, near unity
    - hsCRP acceptable

Wave IV Biomarkers – Challenges

- Digit Preference
  - Took steps to decrease it
    - automated data collection
    - automated range checks
    - conducted post-encounter participant interviews
  - Screened for it
    - overall
    - FI-specific

Digit Preference

- Screening Methods
  - Chi square test statistic
    - H_0: terminal digits ~ *U*
  - Digit preference score (DPS)
    - $\text{DPS} = 100 \times \sqrt{X^2/N(k-1)}$, range 0-100
    - N = number of observations
    - k = number of terminal digits
  - Digit preference indicated by
    - P < 0.05 and
    - DPS ≥ 20 (guards against type I error inherent in testing H_0)

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Digit Preference

DIGIT PREFERENCE IN ANTHROPOMETRIC VARIABLES
ADD HEALTH WAVE IV, MAIN STUDY (2008-2009)

Variable	k	N	ChiSq	P	DPS
WEIGHT (kg)	10	15204	608.4	0.000	6.7
HEIGHT (cm)	10	15373	63.4	0.000	2.1
WAIST (cm)	10	15357	26.3	0.002	1.4

Sorted from high to low DPS. DPS = Hense (1991) digit preference score = 100*(Chisq/(n*(k-1)))**0.5. Range = 0-100. Chisq = goodness of fit test stat, where ni = observed cell freq & sum(ni/k) = expected cell freq in cell i. k = number of possible terminal digits, 0-9 by 1 for weight. k = number of possible penultimate digits, 0-9 by 1 for height and waist. p = p value.

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Digit Preference

DISTRIBUTION OF TERMINAL DIGITS,
ADD HEALTH WAVE IV, MAIN STUDY (2008-2009)

Weight	N	%
x.0	2369	(15.6)
x.1	1338	(8.8)
x.2	1426	(9.4)
x.3	1358	(8.9)
x.4	1331	(8.8)
x.5	1717	(11.3)
x.6	1482	(9.8)
x.7	1366	(9.0)
x.8	1484	(9.8)
x.9	1333	(8.8)

Digit Preference

DIGIT PREFERENCE IN CARDIOVASCULAR VARIABLES
ADD HEALTH WAVE IV, MAIN STUDY (2008-2009)

Variable	k	n	ChiSq	p	DPS
SBP2 (mm Hg)	10	15298	19.3	0.023	1.2
SBP1 (mm Hg)	10	15347	12.5	0.187	1.0
SBP3 (mm Hg)	10	15222	11.7	0.230	0.9
DBP1 (mm Hg)	10	15347	67.9	0.000	2.2
DBP3 (mm Hg)	10	15222	61.8	0.000	2.1
DBP2 (mm Hg)	10	15298	45.0	0.000	1.8
PR1 (beat/min)	10	15262	18.7	0.028	1.2
PR3 (beat/min)	10	15137	10.4	0.319	0.9
PR2 (beat/min)	10	15210	10.0	0.349	0.9

Sorted from high to low DPS. DPS = Hense (1991) digit preference score = 100*(Chisq/(n*(k-1)))**0.5. Range = 0-100. Chisq = goodness of fit test stat, where ni = observed cell freq & sum(ni/k) = expected cell freq in cell i. k = number of possible terminal digits, 0-9 by 1 for weight. p = p value.

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Digit Preference

TERMINAL DIGIT PREFERENCE OF BLOOD PRESSURE, ADD HEALTH WAVE IV

Terminal Digit	SBP Measure			DBP Measure		
	1	2	3	1	2	3
	n (%)[b]	n (%)[b]	n (%)[b]	n (%)[b]	n (%)[b]	n (%)[b]
0	1606 (10.5)	1630 (10.7)	1626 (10.7)	1591 (10.4)	1637 (10.7)	1599 (10.5)
1	1545 (10.1)	1517 (9.9)	1519 (10.0)	1445 (9.4)	1442 (9.4)	1411 (9.3)
2	1560 (10.2)	1500 (9.8)	1492 (9.8)	1667 (10.9)	1685 (11.0)	1700 (11.2)
3	1590 (10.4)	1554 (10.2)	1462 (9.6)	1753 (11.4)	1628 (10.6)	1682 (11.1)
4	1538 (10.0)	1598 (10.5)	1560 (10.3)	1558 (10.2)	1468 (9.6)	1490 (9.8)
5	1491 (9.7)	1453 (9.5)	1502 (9.9)	1476 (9.6)	1467 (9.6)	1476 (9.7)
6	1509 (9.8)	1533 (10.0)	1525 (10.0)	1419 (9.3)	1529 (10.0)	1508 (9.9)
7	1500 (9.8)	1445 (9.5)	1527 (10.0)	1506 (9.8)	1478 (9.7)	1445 (9.5)
8	1552 (10.1)	1533 (10.0)	1507 (9.9)	1476 (9.6)	1503 (9.8)	1442 (9.5)
9	1456 (9.5)	1535 (10.0)	1502 (9.9)	1456 (9.5)	1461 (9.6)	1469 (9.7)
Pearson χ^2	12.49	19.26	11.71	67.90	44.99	61.76
P value	0.187	0.023	0.230	<0.001	<0.001	<.0001
DPS[a]	0.95	1.2	0.9	2.2	1.8	2.1

[a]DPS = digit preference score. [b]Unweighted sample size and percent.

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Digit Preference

FIELD INTERVIEWERS WITH MOST EXTREME FORMS OF DIGIT PREFERENCE

VARIABLE	OBS	K	FI	FI(N)	CHISQ	P	DPS	VARIABLE	OBS	K	FI	FI(N)	CHISQ	P	DPS
WEIGHT_KG	1	10	167	71	945	< 0.001	86.0	HEIGHT_CM	1	10	454	26	181.8	< 0.001	62.3
	2	10	321	83	924.8	< 0.001	78.7		2	10	162	33	226.7	< 0.001	61.8
	3	10	185	34	233.2	< 0.001	61.7		3	10	388	31	96.1	< 0.001	41.5
PR3	1	10	122	111	261.1	< 0.001	36.1	WAIST_CM	1	10	122	111	159.4	< 0.001	28.2
	2	10	454	25	37.2	< 0.001	28.8		2	10	395	25	34	< 0.001	27.5
	3	10	456	34	39.1	< 0.001	25.3		3	10	371	30	37.3	< 0.001	26.3
DBP2	1	10	122	111	327	< 0.001	40.5	SBP1	1	10	122	111	360.9	< 0.001	42.5
	2	10	471	26	41.8	< 0.001	29.9		2	10	379	25	35.6	< 0.001	28.1
	3	10	188	27	41.6	< 0.001	29.2		3	10	324	37	49.8	< 0.001	27.3
SBP2	1	10	122	111	228.3	< 0.001	33.8	DBP1	1	10	122	111	300	< 0.001	38.7
	2	10	431	26	37.2	< 0.001	28.2		2	10	431	26	48	< 0.001	32
	3	10	283	27	35.6	< 0.001	27.1		3	10	154	26	34.2	< 0.001	27
SBP3	1	10	122	111	416	< 0.001	45.6	PR1	1	10	122	111	247.4	< 0.001	35.2
	2	10	241	28	82.6	< 0.001	40.5		2	10	164	31	41.9	< 0.001	27.4
	3	10	222	27	44.5	< 0.001	30.3		3	10	216	42	51.2	< 0.001	26
PR2	1	10	425	31	72.8	< 0.001	36.1	DBP3	1	10	122	111	402.3	< 0.001	44.9
	2	10	122	111	256	< 0.001	35.8		2	10	466	31	31.5	< 0.001	23.8
	3	10	449	27	31.2	< 0.001	25.3		3	10	458	31	30.3	< 0.001	23.3

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Digit Preference

FI 122		
SBP3	n	%
95	1	(1)
99	1	(1)
100	2	(2)
101	1	(1)
105	1	(1)
108	3	(3)
110	9	(8)
112	4	(4)
113	1	(1)
114	2	(2)
115	3	(3)
116	5	(5)
118	15	(14)
119	2	(2)
120	36	(32)
122	5	(5)
124	6	(5)
128	6	(5)
130	5	(5)
132	1	(1)
134	2	(2)

FI 122		
DBP3	n	%
60	5	(5)
61	1	(1)
62	4	(4)
64	2	(2)
65	4	(4)
67	2	(2)
68	2	(2)
69	6	(5)
70	32	(29)
72	9	(8)
74	5	(5)
75	11	(10)
76	2	(2)
78	4	(4)
79	1	(1)
80	16	(14)
82	2	(2)
84	2	(2)
85	1	(1)

Digit Preference

- Summary
  - anthropometric and cardiovascular measures
    - overall, mild
    - FI-specific
      - consistent & severe in rare cases
      - affects relatively few participants
      - highly suspect FI data has been flagged & deleted

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Wave IV Biomarkers – Challenges

- Trend / Cyclicity
  - Took steps to decrease it
    - standardized protocols
    - calibrated, tested equipment
    - used same source & type of supplies, reagents, assays
    - (randomized order of participant examinations)
  - Monitored it

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Trend / Cyclicity

- Monitoring Methods
  - plotted measures versus time
  - compared plots of measures & external standards
  - modeled non-linear associations of measures with time
  - identified best fitting models
  - evaluated generalizability of models across
    - gender
    - race / ethnicity
  - de-trended / de-cycled measures

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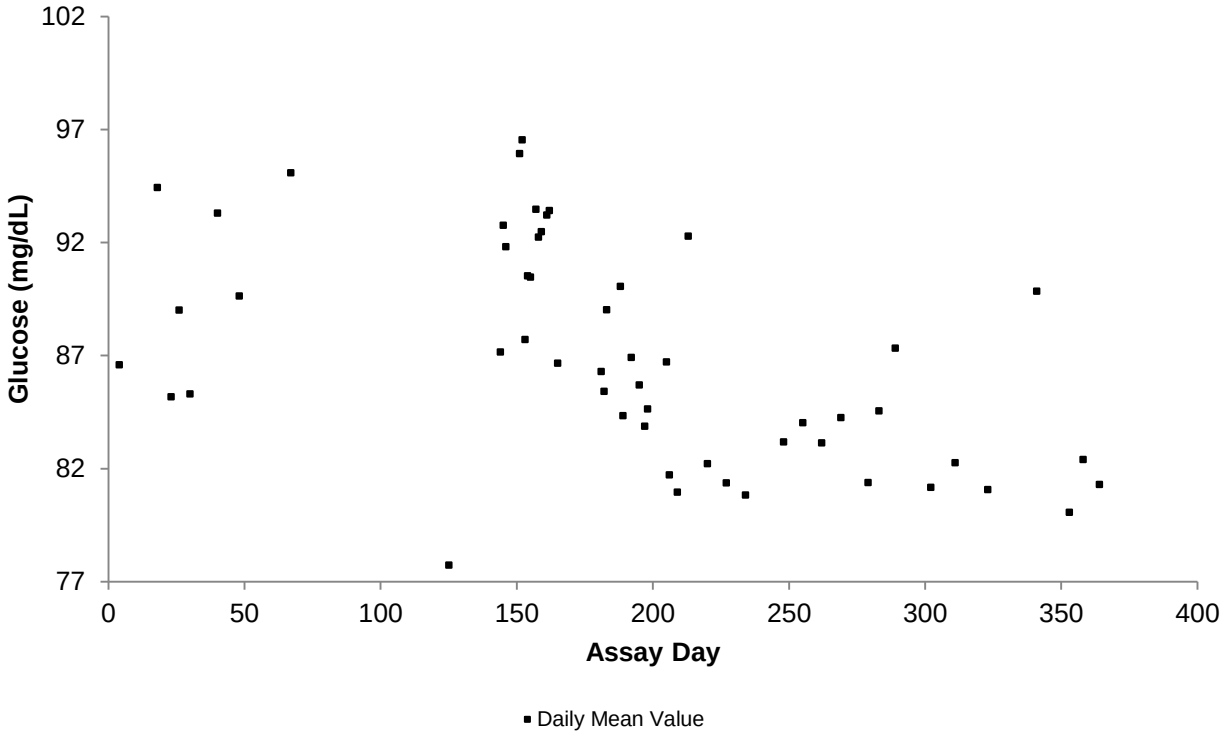
Trend / Cyclicity



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Trend / Cyclicity

- Glucose Standardization Protocol (Apr 2008 - Jul 2008)
  - identified 3 donors
  - assayed glucose @ DUSL
  - spotted 20 cards from a single finger stick/donor
    - donor 1
    - donor 2
    - donor 3

    } x 20 cards = 60 cards
  - sent 1 card/donor to UW lab, 2x/wk x 10 wk
  - masked lab & technicians to origin of card
  - processed the spots per Add Health protocol

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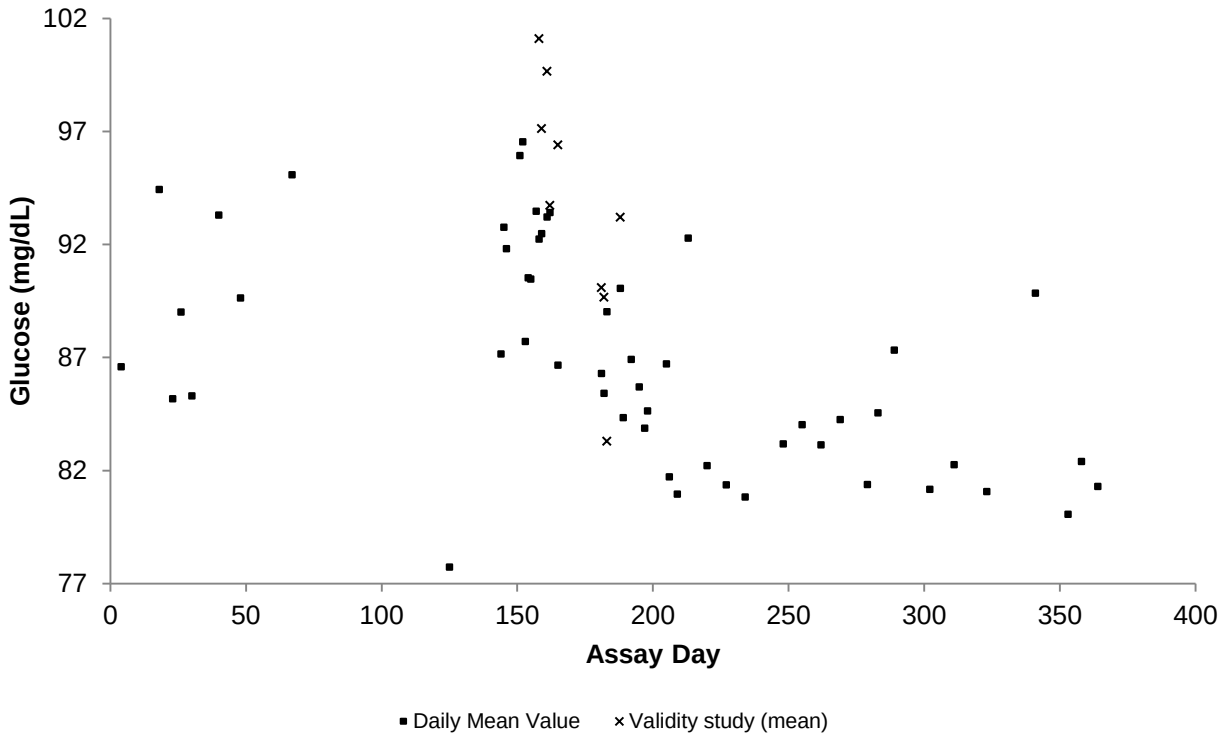
Trend / Cyclicity



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Trend / Cyclicity

Model	AIC	Description
sin(2π*day366/366) + cos(2π*day366/366) + sin(4π*day366/366) + cos(4π*day366/366) + age + sex + race indicators	92606.57	two harmonics + covariates
sin(2π*day366/366) + cos(2π*day366/366) + sin(4π*day366/366) + cos(4π*day366/366) + age + sex + race indicators + day366	92608.05	two harmonics + covariates + linear term
day366 + knots at (100, 220)	92765.68	linear spline
sin(2π*day366/366) + cos(2π*day366/366) + sin(4π*day366/366) + cos(4π*day366/366)	92768.43	two harmonics
sin(2π*day366/366) + cos(2π*day366/366) + sin(4π*day366/366) + cos(4π*day366/366) + day366	92769.50	two harmonics + linear term
sin(2π*day366/366) + cos(2π*day366/366) + day366	92778.16	one harmonic + linear term
day366 + $day366^2$ + $day366^3$	92867.86	polynomial terms
spring + summer + autumn (winter referent)	92881.97	seasons
day366	92896.47	interval-scale assay day

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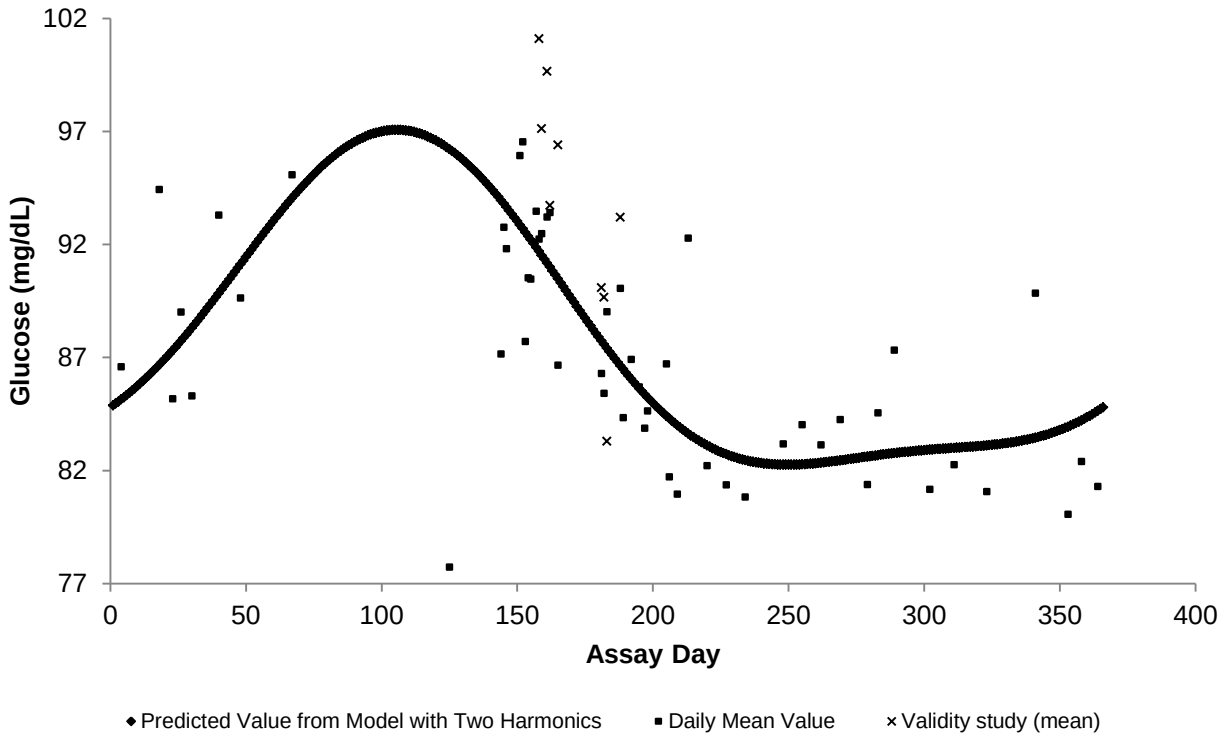
Trend / Cyclicity



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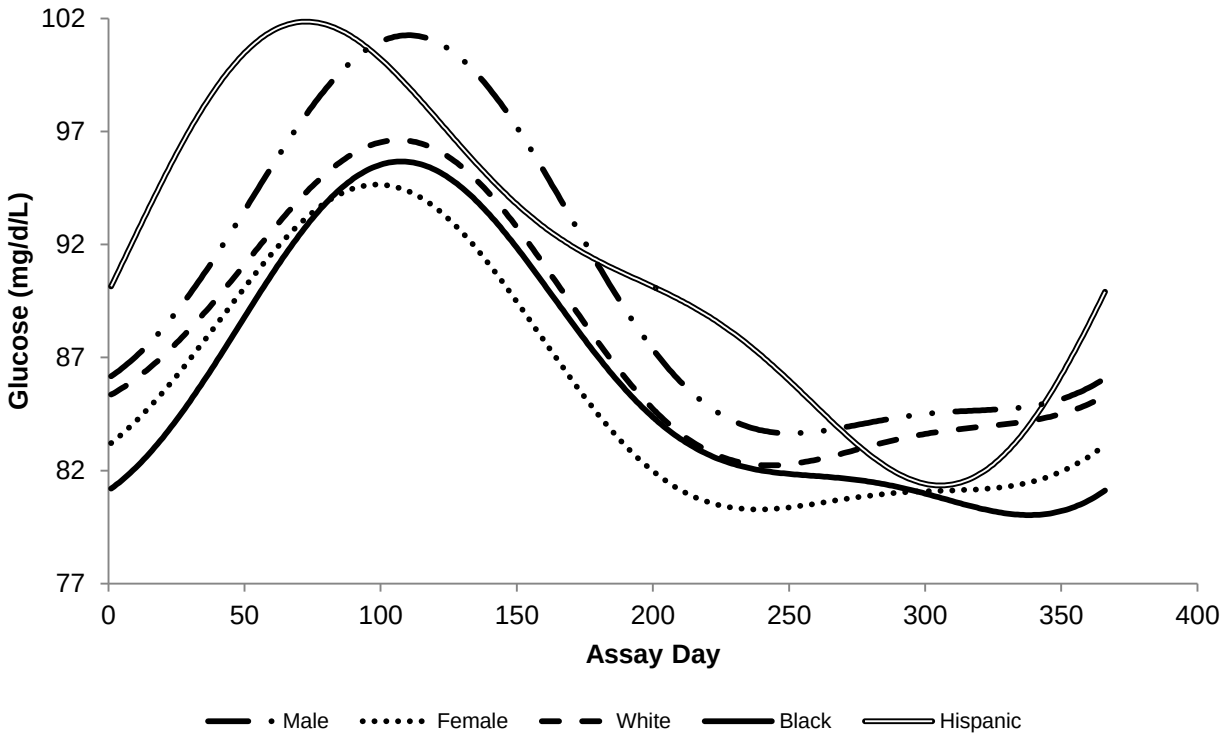
Trend / Cyclicity



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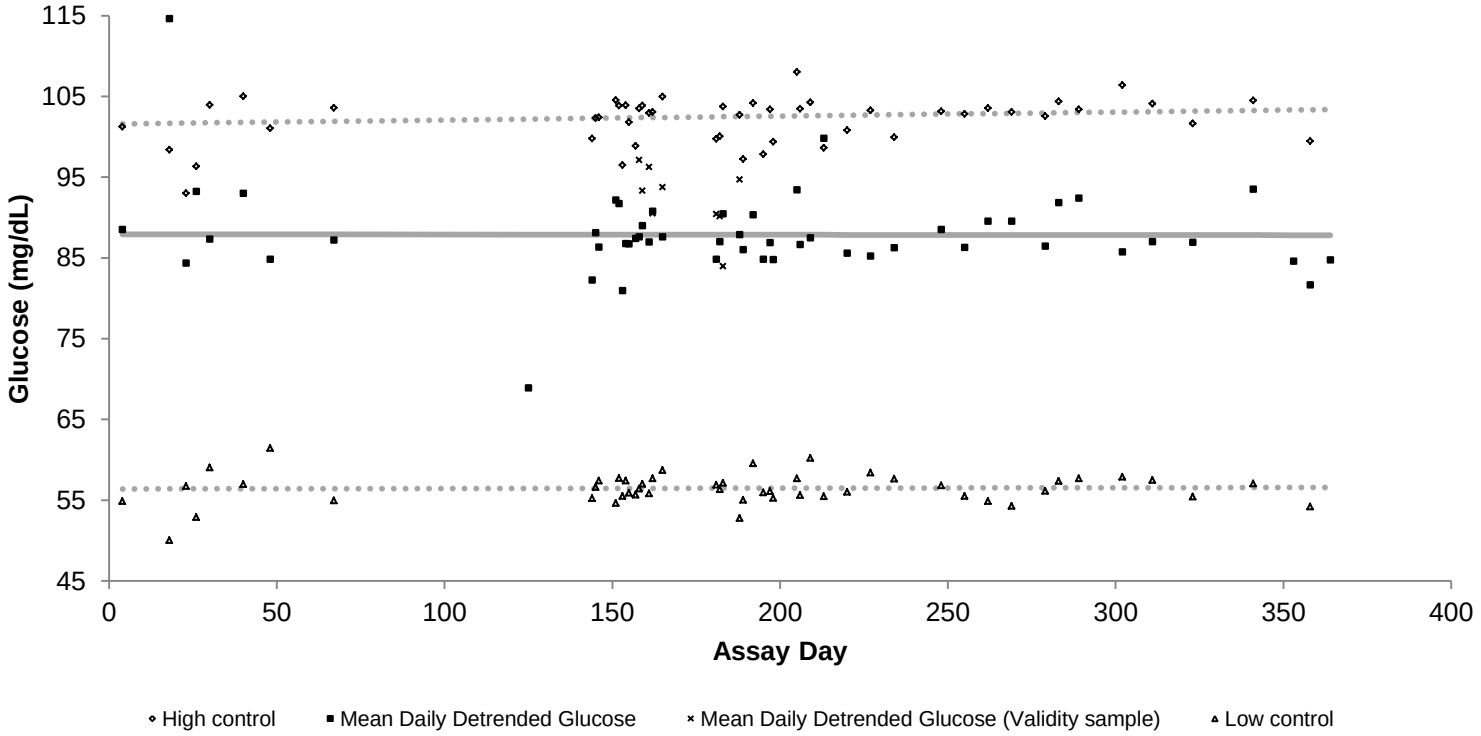
Trend / Cyclicity



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Trend / Cyclicity

- Lipid Standardization Protocol (Apr 2008 - Jul 2008)
  - procured 3 CDC LSP plasma pools, together representing
    - low
    - medium
    - high

    } TG, TC & HDL-C concentrations
  - mixed each pool with washed RBCs
  - spotted 20 cards with each plasma-RBC mixture
    - pool 1
    - pool 2
    - pool 3

    } x 20 cards = 60 cards
  - sent 1 card/pool to the lab, 2x/wk x 10 wk
  - masked lab & technicians to origin of card
  - processed the spots per Add Health protocol

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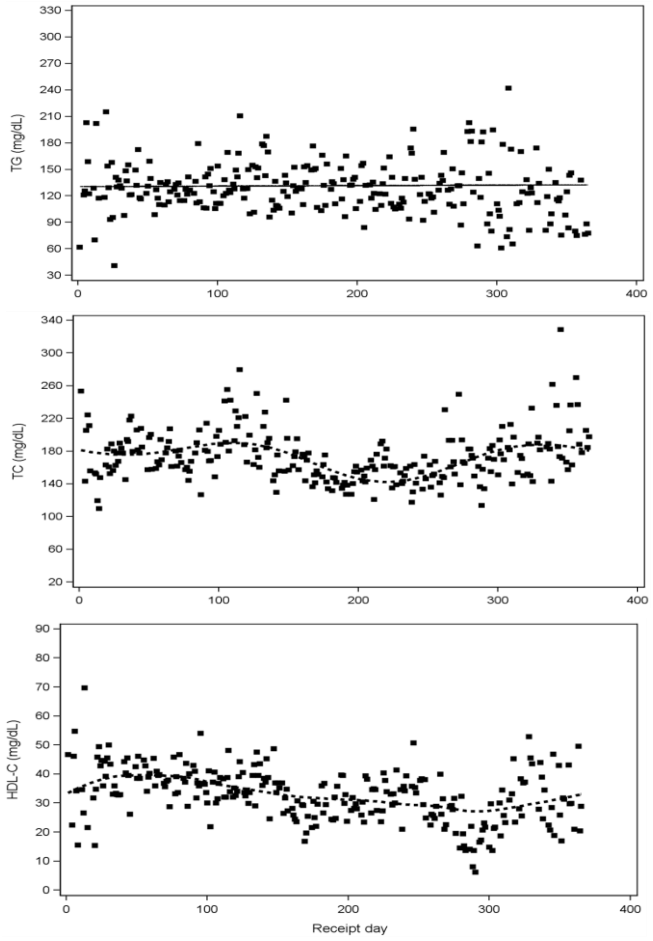
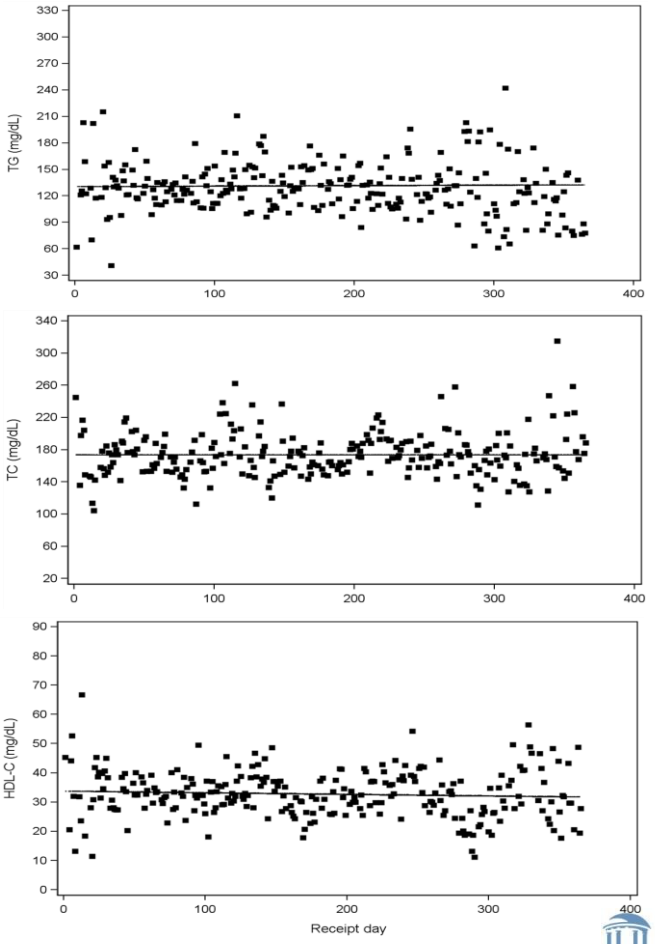
Trend / Cyclicity





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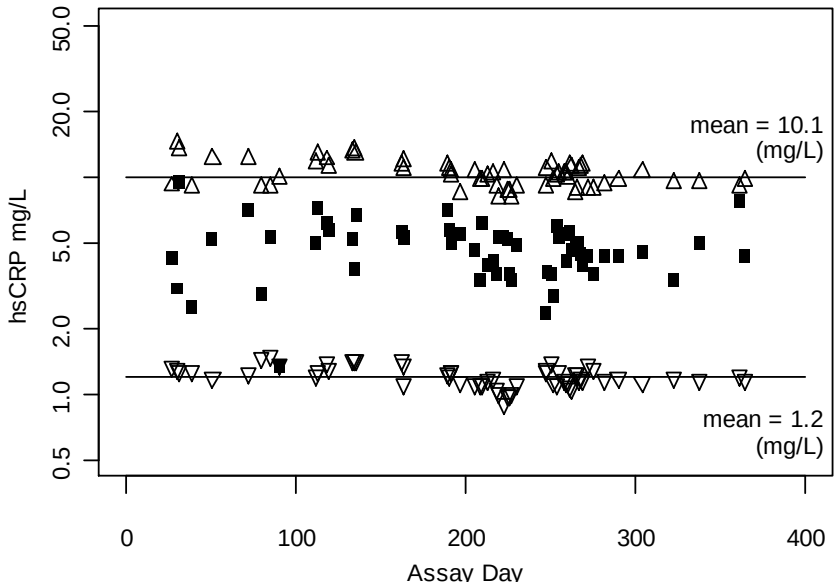
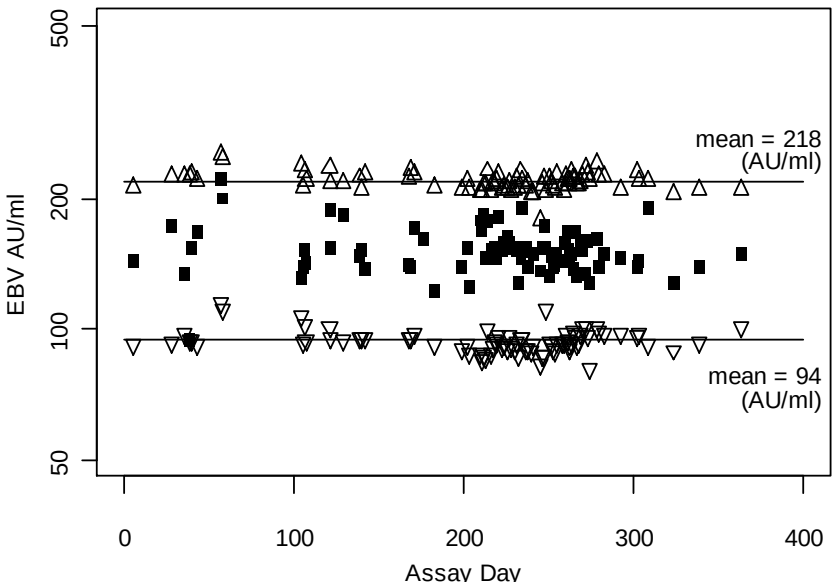
Trend / Cyclicity





△ High control ■ Participants ▽ Low control

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Trend / Cyclicity

- Summary
  - metabolic measures
    - glucose, TC & HDL-C: moderate to severe
    - HbA_{1c} & TG: mild to none
  - immune / inflammatory measures
    - EBV & hsCRP: mild to none
  - trend / cyclicity attenuated, when indicated

Wave IV Biomarkers – Challenges

- Comparability
  - Took steps to increase it
    - standardized protocol
    - calibrated, tested equipment
    - used same source & type of supplies, reagents, assays
  - Evaluated it

Comparability

- Evaluation Methods
  - plotted measures versus time
  - compared related measures in same participant samples
  - modeled associations of measures with one another
  - interconverted measures
  - flagged interconversions

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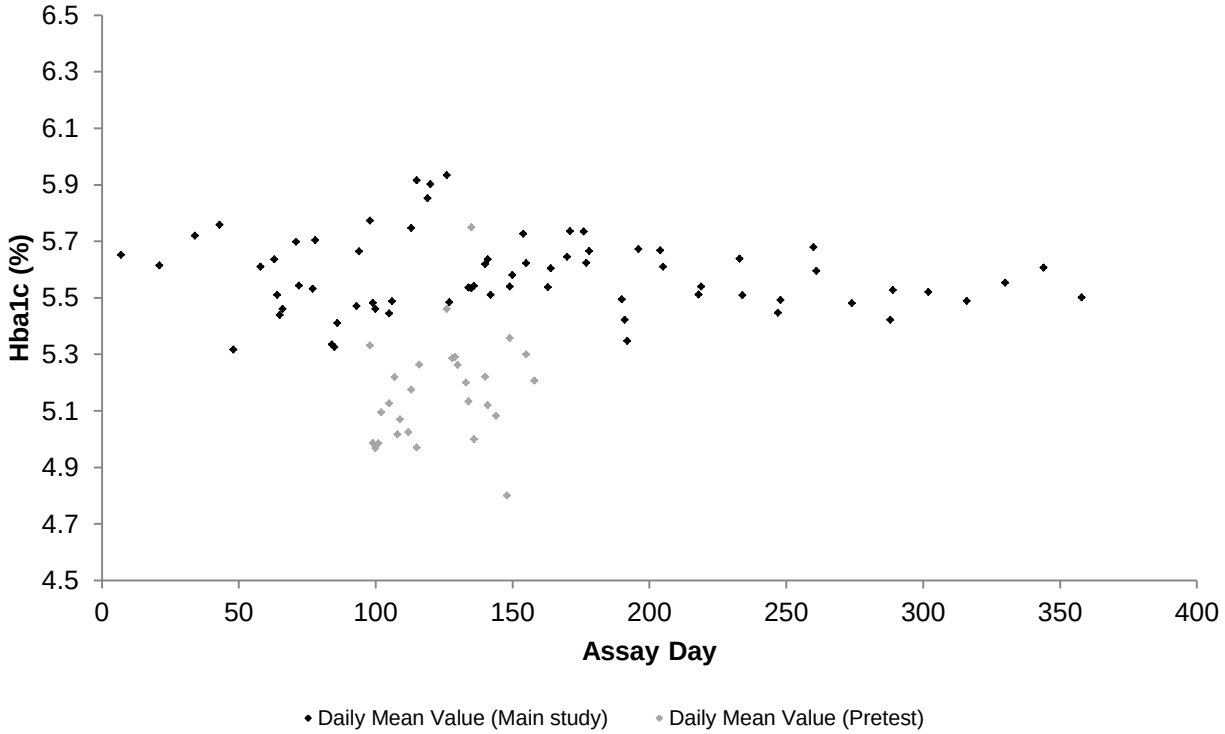
Comparability



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Comparability

- Evaluation Protocol
  - identified a race/ethnicity-, gender- & biomarker-stratified random sample of 96 Main Study participants
    - 4 race/ethnic groups: NHW, NHB, Hispanic & other
    - 3 biomarker concentrations: low, medium & high
    - two genders: male & female
    - 4 x 3 x 2 = 24 groups
    - 4 participants / group
  - resubmitted previously assayed cards for new assay
  - masked labs & technicians to participant identity
  - processed the cards
  - analyzed paired assay results
  - compared w/ analysis in large convenience sample

Comparability

- Analysis Method
  - Deming regression

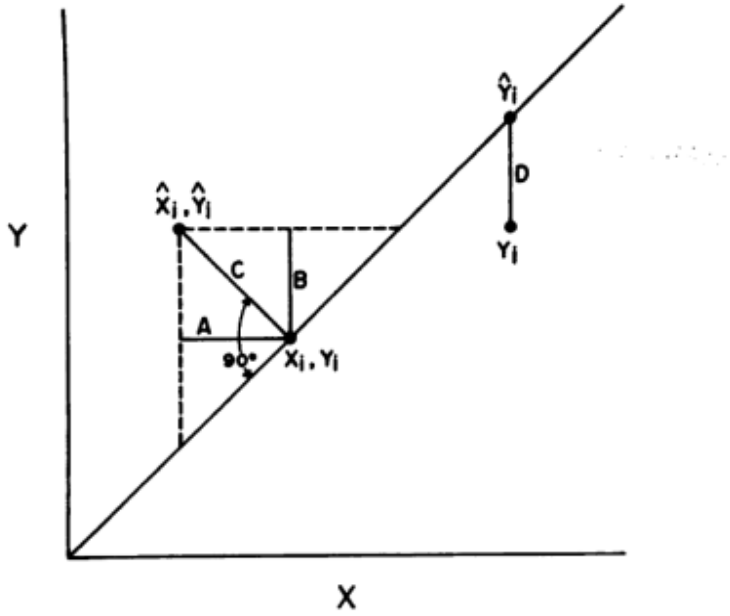

Fig. 1. Least-squares vs. Deming regression model

In the least-squares analysis, the line is chosen to minimize the residual errors in the y direction, i.e., $\Sigma_{i=1}^{N} D^2 = \Sigma_{i=1}^{N} (y_i - \hat{y}_i)^2$ for all data points is minimized. However, in the Deming regression model, the sum of the squares of both the x residual, $A^2 = (x_i - \hat{x}_i)^2$ and the y residual, $B^2 = (y_i - \hat{y}_i)^2$ is minimized. This results in choosing the line that minimizes the sum of the squares of the perpendicular distances from the data points to the line, because geometrically $C^2 = A^2 + B^2$

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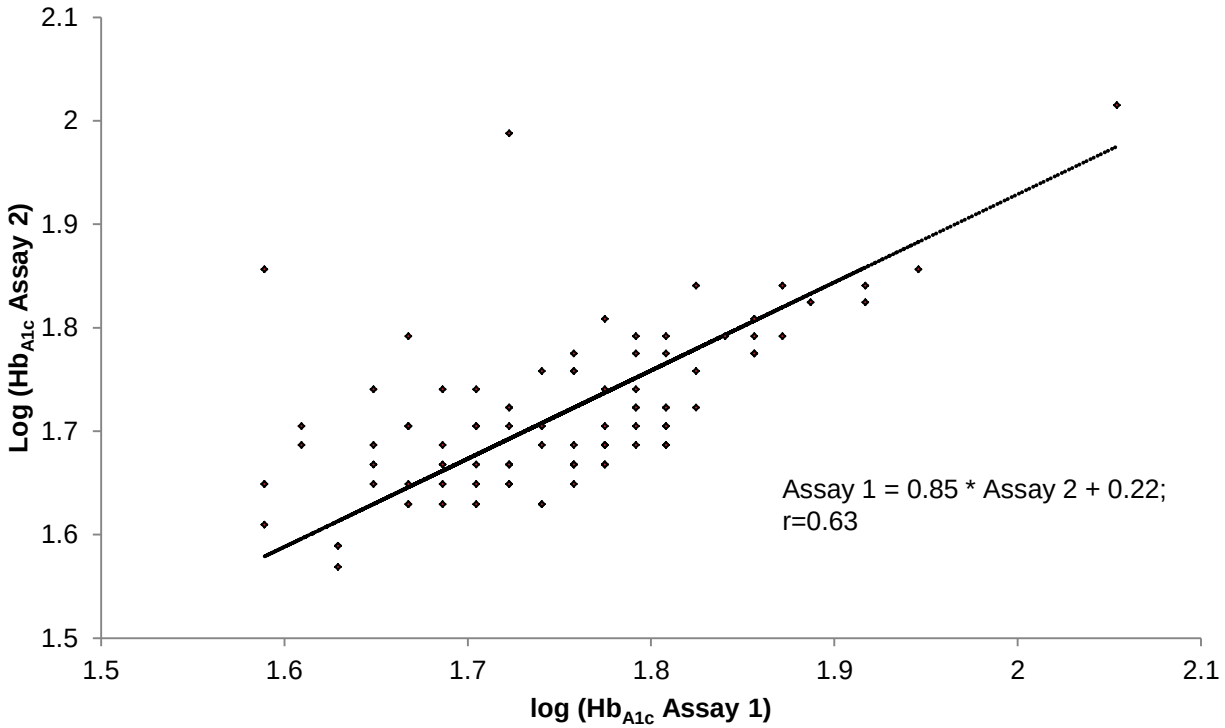
Comparability



Slope (95% CI): 0.85 (0.647, 1.059)
Intercept (95% CI): 0.22 (-0.134, 0.582)

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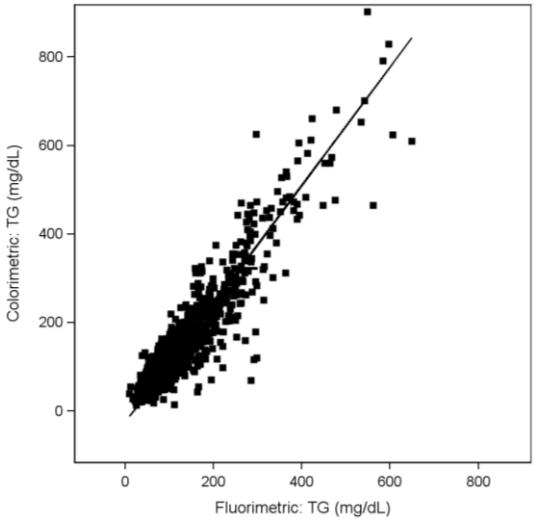
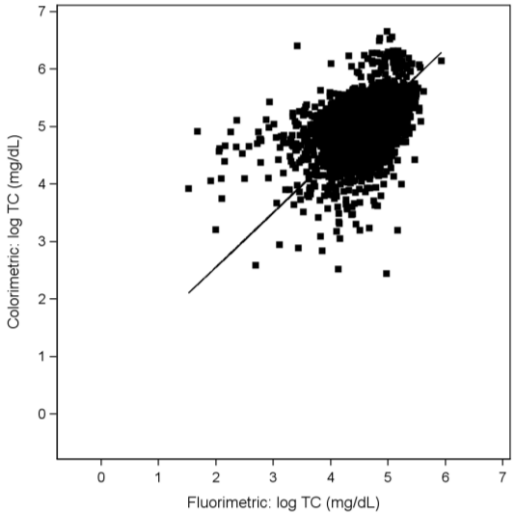
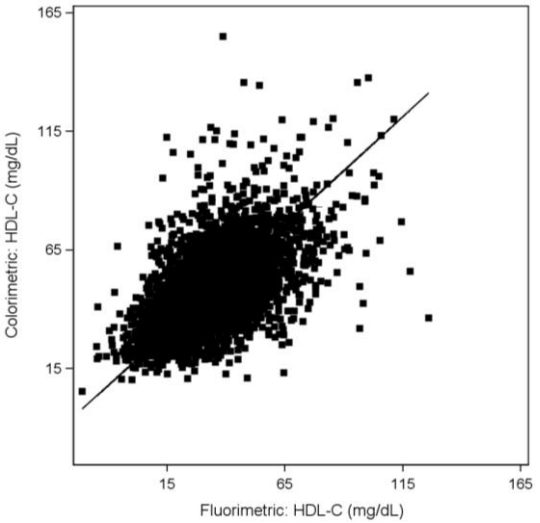
Comparability



TG Assay 1 = 1.34 * Assay 2 - 24.12
r = 0.92
Slope: 1.34 (1.27, 1.40)
Intercept: -24.12 (-31.10, -17.15)



TC Assay 1 = 0.95 * Assay 2 + 0.66
r = 0.47
Slope: 0.95 (0.86, 1.04)
Intercept: 0.66 (0.25, 1.08)



HDL-C Assay 1 = 0.91 * Assay 2 + 17.05
r = 0.55
Slope: 0.91 (0.85, 0.97)
Intercept: 17.05 (15.25, 18.85)

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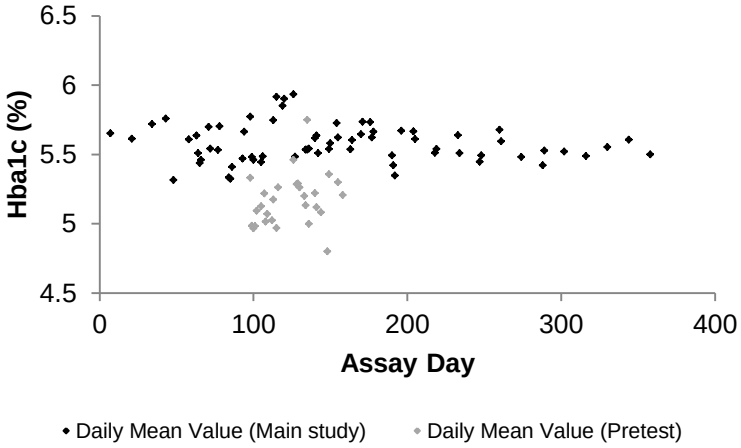
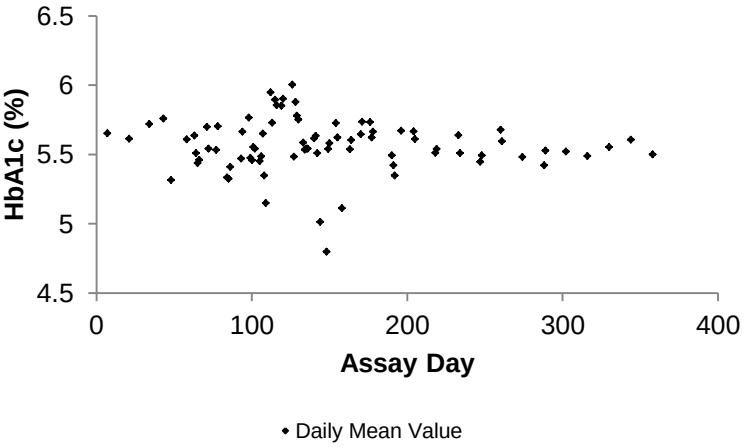
Comparability





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Comparability

- Summary
  - metabolic measures
    - 1st & 2nd generation assays are comparable
    - TG > HbA_{1c} > HDL-C > TC
    - interconversion effected via Deming regression
    - interconversions flagged in released data files

Wave IV Biomarkers – Challenges

- Validity
  - Took steps to increase it
    - standardized protocol
    - calibrated, tested equipment
    - uniformly trained & certified staff
    - automated data collection
    - automated range checks
    - duplicated data entry
    - conducted post-encounter participant interviews
  - Measured it
    - conducted external validation studies

Validity

- BP External Validation Protocol 1 (Dec 2008 – Jul 2009)
  - involved two technicians
  - inspected 292 monitor/cuff pairs returned from the field
    - damage
    - missing parts
    - electronic malfunction
  - attached large adult cuff to 37 cm rigid cylinder
  - connected in tandem with
    - BP monitor (MicroLife 3MC1-PC_IB)
    - pressure meter (Netech DigiMano, Model 2000)
  - recorded pressures over 280-40 mm Hg in 20-unit dec
  - attached adult cuff to 28.5 cm rigid cylinder
  - repeated pressure recordings
  - estimated
    - bias (mm Hg) = meter - monitor pressure
    - relative bias (%) = 100 x bias / meter pressure

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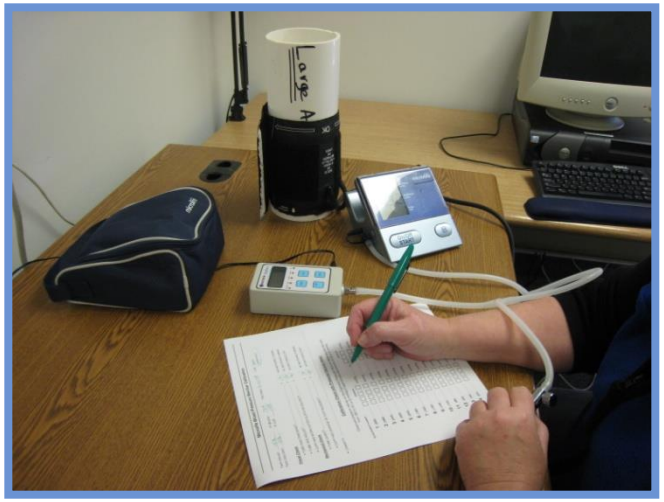
Validity



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Validity

Microlife Blood Pressure Monitor Calibration

Tech ID: _____ FI Cuff: _____ FI Monitor: _____ Test Date: _____ Cuff: ADULT or LARGE ADULT

Visual Check

- TUBE HAS CRACKING? ..... Y N NO MATCHING TUBING
- TUBE HAS HOLES? ..... Y N NO MATCHING TUBING
- CUFF HAS WORN OUTER CLOTH OR VELCRO? ..... Y N NO MATCHING CUFF
- TUBE LEAKS? ..... Y N NO MATCHING TUBING
- CUFF HAS LEAKAGE OF CUFF BLADDER? ..... Y N NO MATCHING CUFF

- *COMMENTS:* _____

Calibration Check with Pressure-Vacuum Meter

Observed pressure values on the Digimano Pressure-Vacuum Meter and the Microlife from 280 to 40 (± 2) mmHg in approximate decrements of 20 (± 2) mmHg.

MEASUREMENT NUMBER	DIGIMANO	MICROLIFE
1 (280)	□□□.□ mmHg	□□□ mmHg
2 (260)	□□□.□ mmHg	□□□ mmHg
3 (240)	□□□.□ mmHg	□□□ mmHg
4 (220)	□□□.□ mmHg	□□□ mmHg
5 (200)	□□□.□ mmHg	□□□ mmHg
6 (180)	□□□.□ mmHg	□□□ mmHg
7 (160)	□□□.□ mmHg	□□□ mmHg
8 (140)	□□□.□ mmHg	□□□ mmHg
9 (120)	□□□.□ mmHg	□□□ mmHg
10 (100)	□□□.□ mmHg	□□□ mmHg
11 (80)	□□□.□ mmHg	□□□ mmHg
12 (60)	□□□.□ mmHg	□□□ mmHg
13 (40)	□□□.□ mmHg	□□□ mmHg

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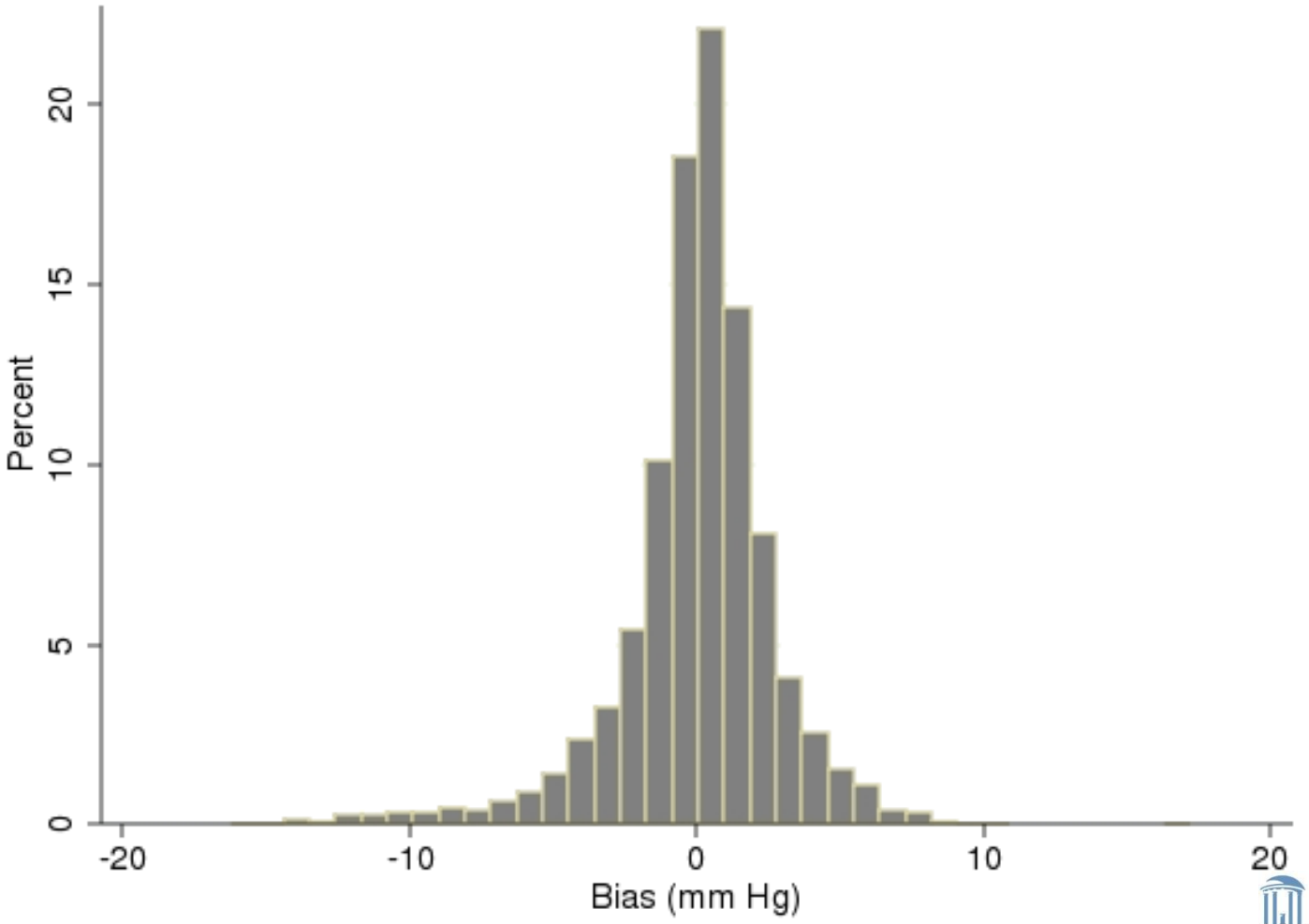
Validity



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Accuracy of Monitor Pressure, by Meter Pressure (mm Hg), Add Health Wave IV (2008-2009)

	Bias (mm Hg)[a]			Relative Bias (%)[b]		
Meter Pressure (mm Hg)	Median	Mean	SD	Median	Mean	SD
280	1.70	1.79	1.78	-0.60%	0.64%	0.64%
260	1.30	1.34	1.89	0.50%	0.51%	0.73%
240	1.10	1.20	1.89	0.46%	0.50%	0.79%
220	1.10	1.26	2.15	0.50%	0.57%	0.98%
200	1.10	1.38	2.16	0.55%	0.69%	1.08%
180	0.70	0.57	2.66	0.39%	0.31%	1.48%
160	0.30	0.06	2.69	0.19%	0.03%	1.68%
140	0.00	-0.28	2.65	0.00%	-0.20%	1.89%
120	-0.40	-0.71	2.59	-0.33%	-0.60%	2.16%
100	-0.60	-1.30	3.27	-0.59%	-1.30%	3.27%
80	-0.75	-1.23	2.74	-0.95%	-1.53%	3.42%
60	-0.70	-1.30	2.73	-1.16%	-2.17%	4.53%
40	-0.90	-1.55	2.53	-2.24%	-3.86%	6.28%

[a]Bias = meter pressure - monitor pressure. [b]Relative bias = 100 × (bias ÷ meter pressure). SD = standard deviation.

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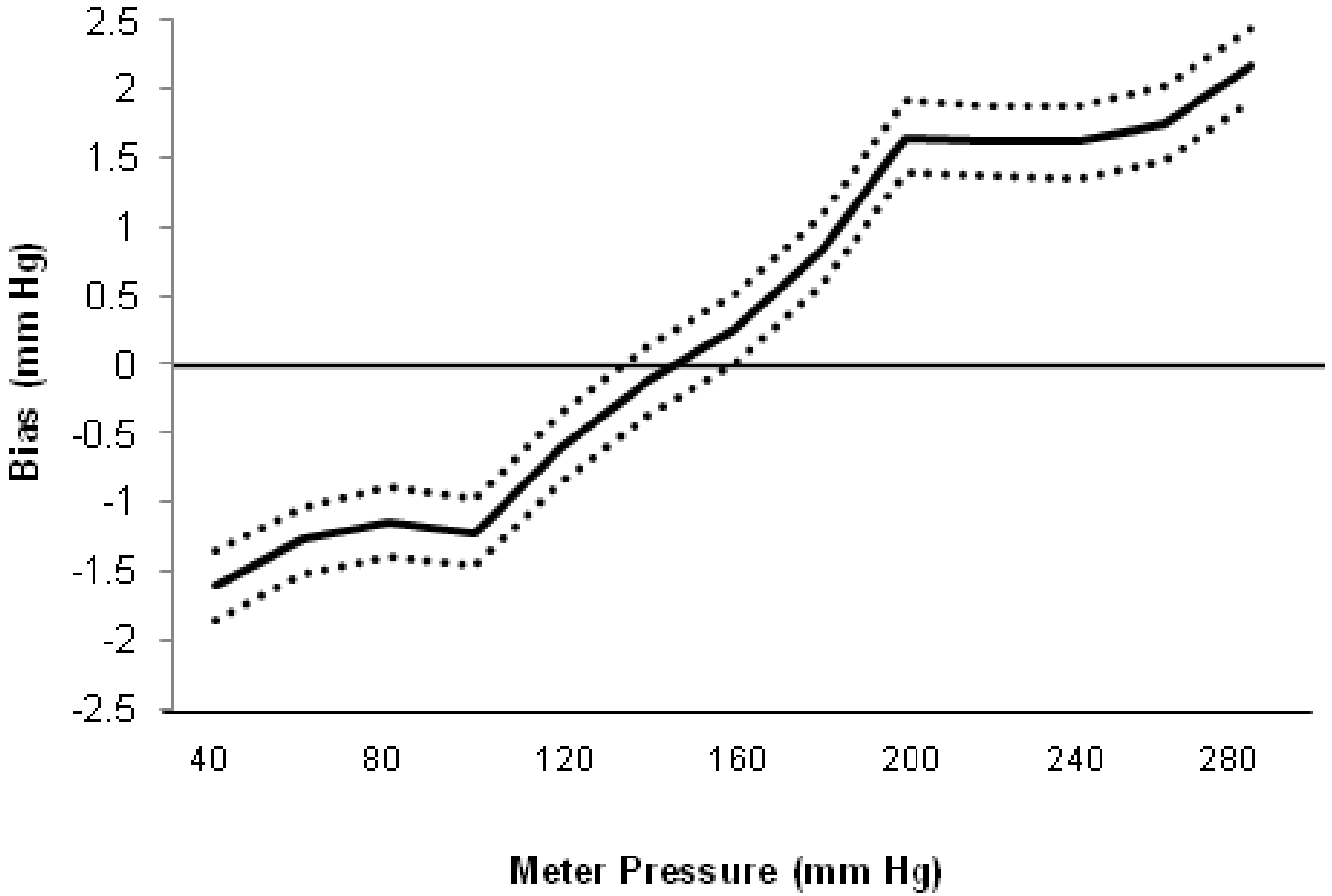
Validity

- Analysis Methods
  - multi-level, random-intercept model
  - $Y_{ijk} = \beta_0 + \beta_1 P_{ijk} + \beta_2 C_{ijk} + \gamma_{1k} + \gamma_{2j(k)} + \varepsilon_{ijk}$
  - where
    - *i* = i[th] cuff pressure (level 1)
    - *j* = j[th] cuff (level 2)
    - *k* = k[th] monitor (level 3)
  - and
    - Y_{ijk} = bias (mm Hg)
    - β_0 = intercept
    - P_{ijk} = vector of meter pressure categories (1-13)
    - C_{ijk} = vector of covariates, e.g. technician ID
    - $\gamma_{1k} + \gamma_{2j(k)}$ = random intercepts @ levels 3 & 2
    - ε_{ijk} = random error @ level 1

Validity


2.5
2
1.5
1
0.5
0
-0.5
-1
-1.5
-2
-2.5
Bias (mm Hg)
40
80
120
160
200
240
280
Meter Pressure (mm Hg)

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Validity

- BP External Validation Protocol 2 (April 2011)
  - convenience sample (n = 22)
    - 24-32 years
    - 55% female
    - 27% black / 27% white / 23% Hispanic / 23% other
    - BMI 18-33 kg/m^2
  - two technicians
    - A: recorded BP via Add Health protocol x 3
      - oscillometric BP monitor (MicroLife 3MC1-PC_IB)
    - B: recorded BP via NHANES protocol x 3
      - Hg sphygmomanometer (Standby Baumanometer)
      - stethoscope
      - manual auscultation
    - order of recordings randomized
    - 2^{nd} & 3^{rd} values averaged
    - technicians masked

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Validity

- NHANES - Add Health difference, mean (SD)
  - SBP = -3 (7) mm Hg
  - DBP = 4 (4) mm Hg
- Pearson's r
  - SBP = 0.80
  - DBP = 0.89

Add Health
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Validity

- BRS, PRR & SBPR Validation
  - dichotomized measures at their means
  - estimated association of low values w/ CVD risk factors

Odds Ratio (95% CI) for low BRS, HRR & SBPR by CVD risk factor

CVD Risk Factor		n	BRS	PRR	SBPR
BMI (kg/m^2)	<25	4631	1.00	1.00	1.00
	25-30	4202	1.00 (0.90,1.12)	1.04 (0.91,1.18)	1.57 (1.42,1.73)
	30-35	2568	1.18 (1.05,1.34)	1.04 (0.90,1.21)	1.79 (1.55,2.07)
	35-40	1296	1.12 (0.93,1.35)	1.30 (1.10,1.53)	1.78 (1.51,2.11)
	≥40	1174	1.72 (1.41,2.11)	1.47 (1.22,1.77)	2.11 (1.80,2.47)
HbA1c (%)	<5.7	8586	1.00	1.00	1.00
	5.7-6.4	3752	1.06 (0.94,1.19)	1.04 (0.93,1.15)	1.20 (1.09,1.32)
	≥6.5	555	1.49 (1.17,1.89)	1.36 (1.08,1.71)	1.26 (1.02,1.56)
SBP/DBP	normal	4771	1.00	1.00	1.00
	pre	6669	1.16 (1.05,1.29)	1.03 (0.91,1.16)	2.43 (2.20,2.69)
	stage I	2099	1.67 (1.45,1.92)	1.14 (0.98,1.33)	4.05 (3.49,4.70)
	stage II	464	3.87 (2.90,5.16)	1.41 (1.09,1.81)	6.46 (4.85,8.61)

CVD = cardiovascular disease.

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Validity

- HbA_{1c} & Glucose Validation

Sample	DUSL* HbA_{1c} (%)	n	Bias† Mean (SE)
1	5.4	20	0.12 (0.03)
2	4.9	20	0.23 (0.03)
3	5.4	20	0.24 (0.03)
All	5.2	60	0.20 (0.05)

*Duke University System Laboratory. †Bias = FlexSite HbA_{1c} – DUSL HbA_{1c}. SE = standard error.

Study	n	r (95% CI)*
Add Health	2221	0.68
NHANES	343	0.75

*r (95% CI) = Pearson's correlation (95% confidence interval) for the fasting glucose-HbA_{1c} association among participants with both measures

Study	n	Mean (SD), mg/dl Glucose	EAG*	MPG†	Overestimation (%) EAG*	MPG†
Add Health	2208	107 (35)	116 (28)	124 (34)	108	116
NHANES	309	97 (14)	104 (13)	109 (17)	107	112

*Estimated Average Glucose = 28.7 × HbA1c – 46.7 (Nathan et al., 2008) and †Mean Plasma Glucose = 35.6 × HbA1c – 77.3 (Rohlfing et al., 2002), among participants with both measures.

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Validity

- Lipid Validation

Bias* of lipid measures: Add Health Wave IV

		Mean		Bias (95% CI)*
Lipid	n	CDC	UW	UW-CDC
TG	60	145	176	30 (20,40)
TC	60	203	197	-6 (-34,23)
HDL-C	60	47	63	15 (3,27)

Mean difference (95% confidence interval) estimated in a repeated measures ANOVA allowing for random variation of bias among and an autoregressive correlation structure within lipid concentrations. CDC = Centers for Disease Control Lipids Standardization Program. CI = confidence interval. UW = University of Washington Department of Laboratory Medicine.

Correlation* of Lipid Measures: Add Health, Wave IV

Lipid	n	Pearson	p	Spearman	p
TG	60	0.84930	<.0001	0.78264	<.0001
TC	60	0.66082	<.0001	0.69895	<.0001
HDL-C	60	0.72595	<.0001	0.68010	<.0001

*Between UW- and CDC-determined concentrations. CDC = Centers for Disease Control Lipids Standardization Program. UW = University of Washington.

% in Highest Lipid Decile, by Gender, Fasting Status & History of Hyperlipidemia or Anti-hyperlipidemic Medication Use

	Gender		Fasting		Hyperlipidemia	
Lipid	Male	Female	≥ 9 hr	< 9 hr	Yes	No
TG	14.0	6.6	5.9	11.0	22.2	9.1
TC	10.7	10.1	9.0	10.7	15.6	9.9
HDL-C	6.7	13.5	8.4	10.4	11.0	10.0

Weighted percent of 5971 male & 7148 female, 1994 fasting & 11012 non-fasting, and 1090 hyperlipidemic & 12029 non-hyperlipidemic participants.

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Validity

- hsCRP Validation

hsCRP (mg/L) by Subclinical Symptom Count, Infectious / Inflammatory Disease Count and Anti-Inflammatory Medication Use

Exposure		Mean	(SD)	Median
Subclinical Symptoms*	0	4.2	(7.0)	1.8
	1	5.9	(10.4)	2.5
	2	7.6	(12.3)	3.4
	3+	7.7	(11.7)	3.8
Common Infectious / Inflammatory Diseases*	0	4.6	(8.1)	2.0
	1	5.2	(9.0)	2.2
	2	5.6	(8.6)	2.4
	3+	8.6	(18.0)	3.1
Anti-inflammatory Medication Use	No	4.5	(7.6)	1.9
	Yes	5.9	(10.5)	2.6

*Pearson correlation between hsCRP (mg/L) and counts of subclinical symptoms and infectious/inflammatory diseases = 0.13 and 0.05, respectively.

Validity

- Summary
  - cardiovascular measures
    - BP bias low
    - BP correlation w/ standards high
    - BRS, PRR & SBPR correlation w/ CVD risk factors high
  - metabolic measures
    - HbA_{1c}
      - bias low
      - correlation w/ fasting glucose high
      - overestimation of fasting glucose modest, typical
    - TG, TC & HDL-C
      - bias high
      - correlation w/ standards high
      - anticipated relationship w/ established predictors
    - hsCRP
      - anticipated relationship w/ established predictors

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Wave IV Biomarkers – Challenges

- Scope
- Reliability
- Digit Preference
- Trend / Cyclicity
- Comparability
- Validity

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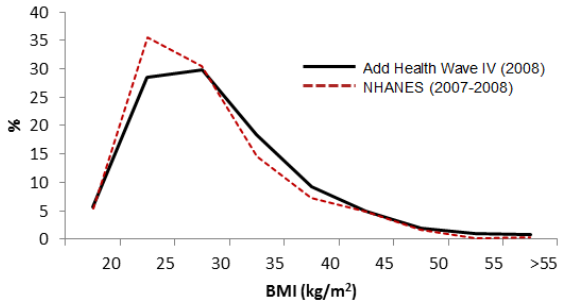
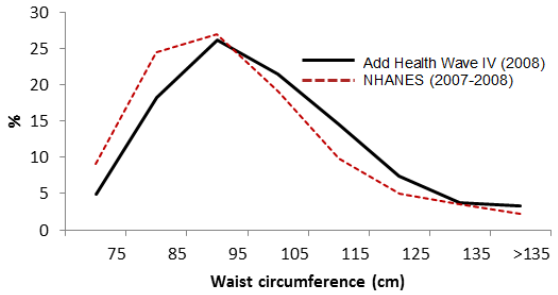
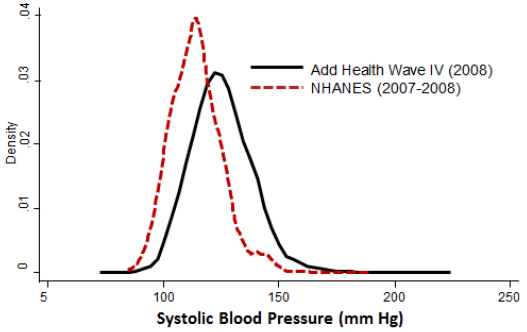
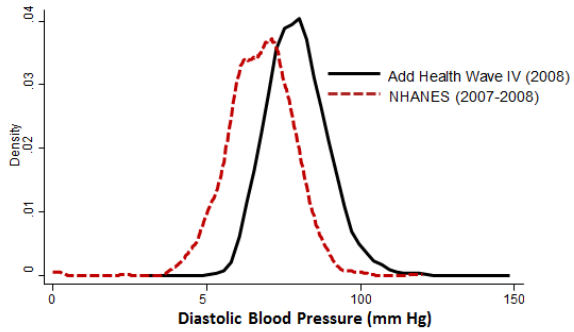
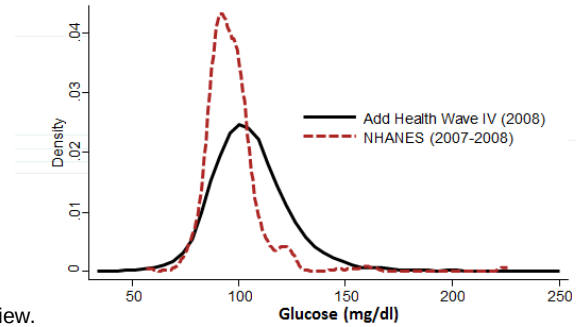
Findings

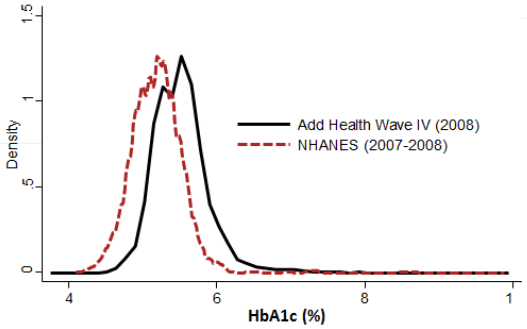












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Nguyen et al. Epidemiol 2011;22(4):532-541.
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Whitsel et al. *Circulation* 2012;125:AP010.

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Resources

- To Learn More
  - General
    - http://www.cpc.unc.edu/projects/addhealth
  - User Guides
    - http://www.cpc.unc.edu/projects/addhealth/data/guides
  - Wave IV Data
    - http://www.cpc.unc.edu/projects/addhealth/data
  - Add Health Staff

KATHIE MULLAN HARRIS	PRINCIPAL INVESTIGATOR
CAROLYN HALPERN	DEPUTY DIRECTOR
LEY KILLEYA-JONES	PROJECT MANAGER
SARAH DEAN	ASSISTANT PROJECT MANAGER
JON HUSSEY	BIRTH RECORDS PROJECT PI
CHIRAYATH SUCHINDRAN	BIOSTATISTICIAN
ERIC WHITSEL	BIOLOGY PROJECT PI
NANCY DOLE	BIOLOGY PROJECT PI
JOYCE TABOR	DATA MANAGER
CARMEN CUTHBERTSON	APPLICATIONS PROGRAMMER
MARIAH CHENG	APPLICATIONS PROGRAMMER
PING CHEN	APPLICATIONS PROGRAMMER
TIM MONBUREAU	APPLICATIONS PROGRAMMER
QUYNH NGUYEN	POSTDOCTORAL FELLOW

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Add Health Wave IV Biomarkers: Update

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