Iron status and novel risk factors for iron depletion in a diverse donor population

Bryan Spencer, Yuelong Guo, Ritchard Cable, Joseph Kiss,
Michael Busch, Grier Page, Stacy Endres-Dighe,
Steve Kleinman, Simone Glynn, Alan Mast,

for the NHLBI Recipient Epidemiology and
Donor Evaluation Study-III (REDS-III)

AABB Annual Meeting
Scientific Plenary Oral Abstract Session
October 9, 2017

REDS-III

Disclosures

- No disclosures

Objectives

- Review prevalence of Low Ferritin and Absent Iron Stores in a large, diverse donor population
- Discuss similarities and differences in risk for iron depletion across race/ethnicity
- Review secondary risk factors for iron depletion

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Background

- Iron depletion is common in blood donor populations.
- Major demographic risk factors and importance of donation frequency are well-established.
- Prior research conducted in homogeneous donor populations.
- Known risk factors might differ across racial/ethnic populations.
- Secondary risk factors might be identifiable.

Participating institutions in REDS-III RBC-Omics

- **Red Blood Cell – Omics study (RBC-Omics)**
- Blood centers
  - Blood Center of the Pacific, San Francisco, CA
  - BloodCenter of Wisconsin, Milwaukee, WI
  - Institute for Transfusion Medicine, Pittsburgh, PA
  - American Red Cross, Connecticut Region, Farmington, CT
- Data coordinating center
  - RTI International, Rockville, MD
- Central Lab
  - Blood Systems Research Institute, San Francisco, CA

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REDS-III RBC-Omics Study

1. **Identify Novel Polymorphisms in Hemoglobin and Iron Regulatory Proteins (Pica and RLS)**
2. **Genetic and Metabolic Basis for Donor-Specific Differences in Storage Hemolysis**
3. **Establish a Sharable Biorepository of RBC, Plasma, WBC, and DNA Samples for BioLINCC**

- Informed of objectives and scope of study
- Informed Consent forms signed
- Questionnaire
- Donate a unit of whole blood to be processed into a LR-RBC component
- Unit/retention tube tagged and tracked by Subject Tracking System (RTI)

cells from 14,000 donations

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- Informed Consent forms signed
- Questionnaire
- Donate a unit of whole blood to be processed into a LR-RBC component
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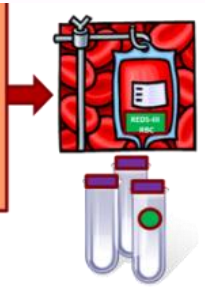
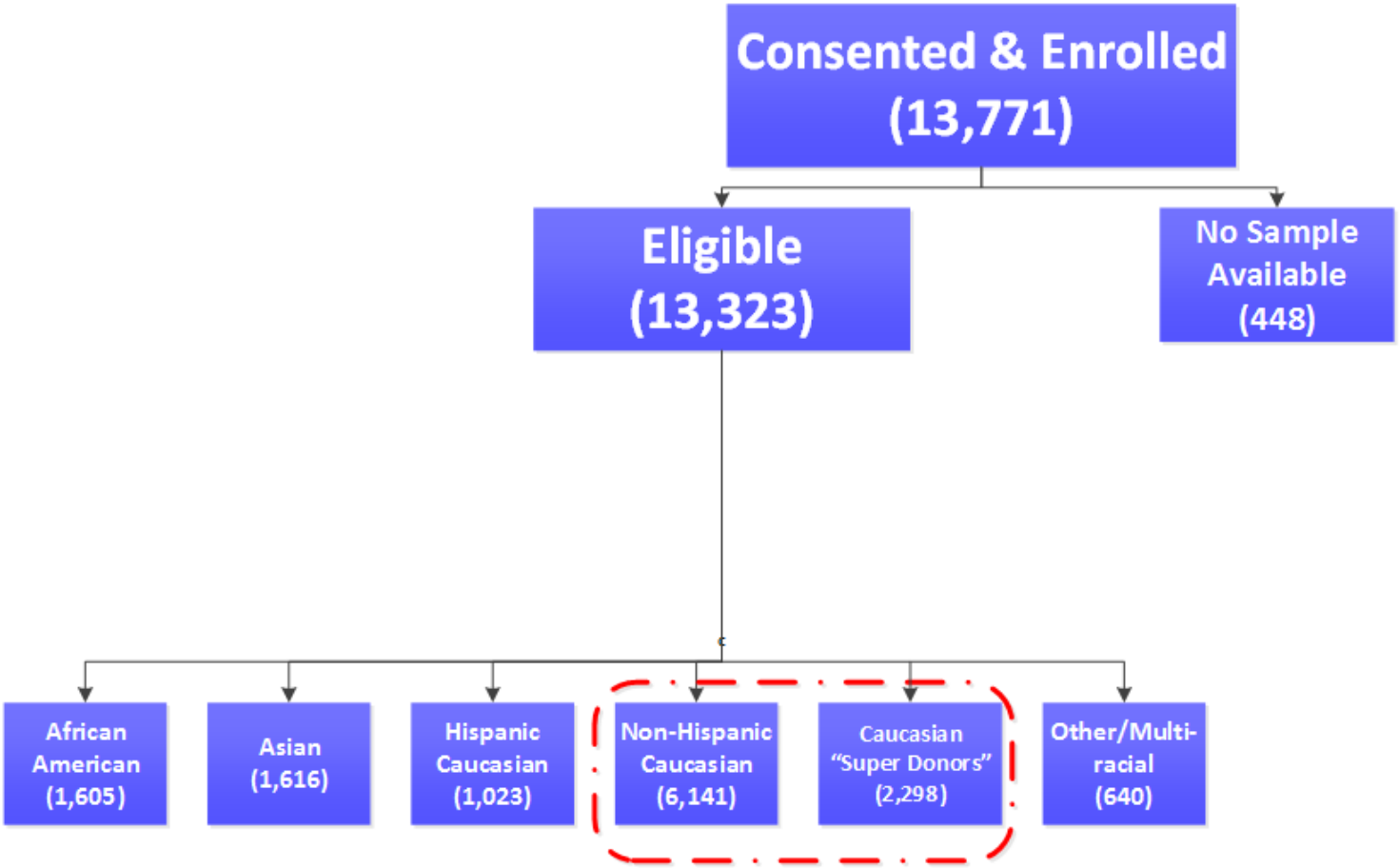


See session 0311-TC “Donor variability, product quality, and transfusion outcome.” Monday, 10:30 , SDCC room 29CD.

This project pursues the overarching hypothesis that genetic variation in donors underlies the variable propensity of erythrocytes to hemolyze during routine RBC storage and after transfusion

Donors eligible for ferritin analysis



Total Non-Hispanic White (NHW) = 8439

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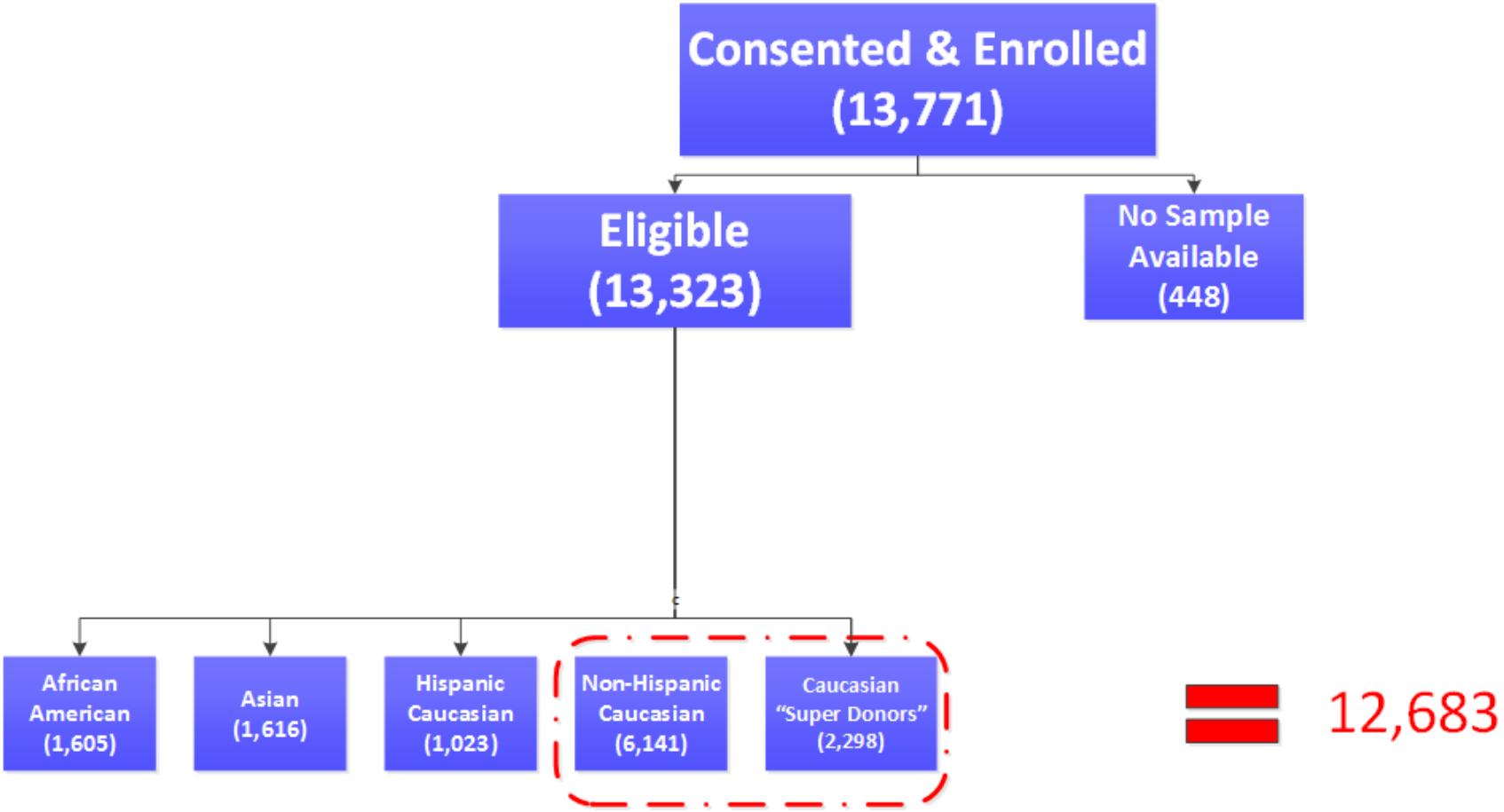
Donors eligible for ferritin analysis



Total NHW 8439

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Ferritin model development

- Outcomes of interest:
  - *ferritin <12ng/mL = Absent Iron Stores*
  - *ferritin <26 ng/mL = Low Ferritin ≈ Iron Deficiency Erythropoiesis (REDS-II RISE)*
- Models stratified by race/ethnicity
  - Covariates include age, sex, donation frequency, weight, iron supplementation, blood center
- Models with pairwise comparisons of each group to NHW
  - Same covariates: allows for direct statistical comparisons
- All-subject models
  - Same covariates, + smoking, antacid use, hormone supplements

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Donor demographics & iron status

	African-American (AA)		Asian (As)		Caucasian-Hispanic (Hisp)		Caucasian-Non-Hispanic (NHW)	
N	**1605**		**1616**		**1023**		**8439**	
Sex	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**
N	862	743	735	881	614	409	4141	4298
Age category								
< 20 years old	82	69	74	50	90	52	133	76
20-29	199	188	246	244	201	135	576	495
30-39	154	110	175	244	132	83	508	499
40-49	151	133	114	170	100	68	620	602
50-59	156	151	82	120	68	51	1144	1176
60+	120	92	44	53	23	20	1160	1450
Iron status								
Ferr < 12 (%)	19.8	4.4	21.0	5.7	30.5	9.5	26.8	15.9
Ferr < 26 (%)	42.6	17.6	42.7	15.7	59.1	19.8	56.7	38.0

Excluding "Super-Donors": Aggregate % ferritin < 12 ≈ 17%
Aggregate % ferritin < 26 ≈ 38%

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Similar risk for ferritin < 26 with more donations

	African-American (AA)	Asian (As)	Caucasian-Hispanic (Hisp)	Caucasian-Non-Hispanic (NHW)
Reference group %	4.1%	10.8%	4.5%	11.3%
0 units donated in last24m	REF (OR=1)	REF (OR=1)	REF (OR=1)	REF (OR=1)
1-2	2.0	2.9	2.5	2.1
3-4	5.6	5.5	8.4	4.7
5-6	11.3	5.1	15.0	9.8
7+	13.9	14.9	25.6	16.5

Reference group is 40yo male with 0 donations, no iron supplementation, 180 lbs weight

Controlling for age, sex, age*sex, weight, blood center, iron supplementation

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Risk for ferritin < 26 mostly similar by age and sex

	African-American (AA)		Asian (As)		Caucasian-Hispanic (Hisp)		Caucasian-Non-Hispanic (NHW)	
Reference group %	4.1%		10.8%		4.5%		11.3%	
F vs M	8.6		6.6		7.3		4.5	
	Female	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**
< 20 yrs old	1.9	3.8	1.5	0.4	4.7	2.8	2.7	1.5
20 to 29	2.4	1.7	1.1	0.9	2.2	2.2	1.4	1.0
30 to 39	1.2	1.5	0.9	1.7	2.2	1.3	0.9	0.9
40 to 49	REF	REF	REF	REF	REF	REF	REF	REF
50 to 59	0.3	1.6	0.2	1.3	0.4	1.1	0.5	1.0
≥ 60 yrs old	0.4	2.8	0.2	1.3	0.3	1.4	0.4	1.0

Controlling for donation frequency, weight, blood center, iron supplementation

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Model results for iron supplementation and medications

	Ferritin < 12 ng/mL		Ferritin < 26 ng/mL	
	Odds Ratio	**95% CI**	**Odds Ratio**	**95% CI**
Iron supplementation (multivitamin with iron or iron-only supplement)				
Daily vs none	0.59	(0.52, 0.66)	0.67	(0.61, 0.75)
Less than daily vs none	0.81	(0.70, 0.94)	0.95	(0.83, 1.08)
Medications				
Antacid use: any vs none	1.24	(1.08, 1.42)	1.21	(1.08, 1.37)
Hormone use: females vs none	0.85	(0.72, 1.0)	0.78	(0.67, 0.90)
Hormone use: males vs none	2.29	(1.35, 3.89)	1.49	(0.92, 2.41)

Logistic regression controlling for age, sex, age*sex, weight, blood center, donations, smoking and race.

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Model results for risk by race/ethnicity

	Ferritin < 12 ng/mL		Ferritin < 26 ng/mL	
	Odds Ratio	95% CI	Odds Ratio	95% CI
Race / ethnicity				
AA vs NHW	0.81	(0.68, 0.96)	0.86	(0.75, 0.99)
Asian vs NHW	0.76	(0.62, 0.91)	0.66	(0.57, 0.77)
Hispanic vs NHW	1.25	(1.04, 1.52)	1.19	(1.01, 1.41)

Logistic regression controlling for age, sex, age*sex, weight, blood center, donations, iron supplementation, smoking and medications.

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Plots of observed values and model residuals - NHW

NHW – Observed frequencies

NHW – Model residuals

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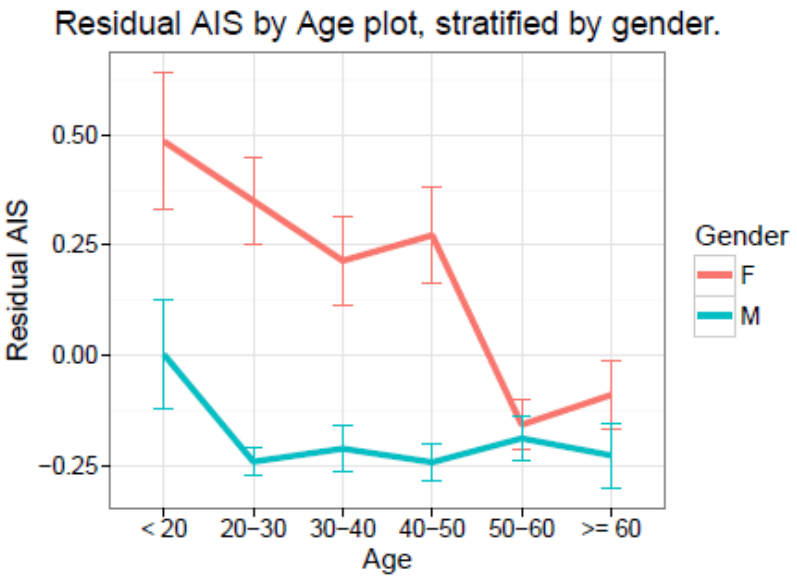
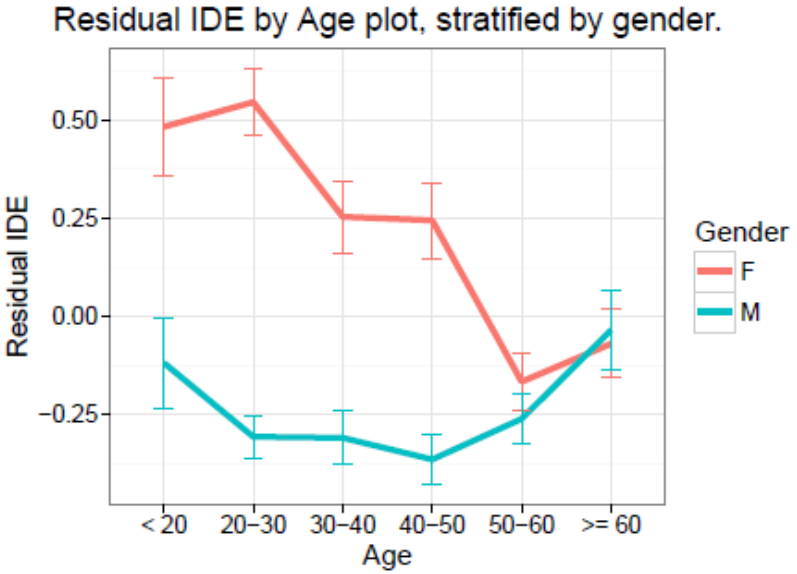
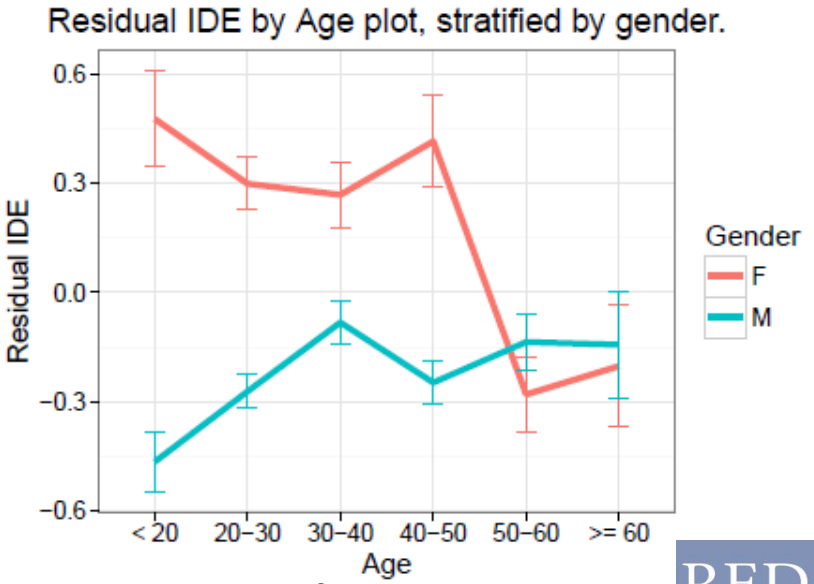
Model residual plots: Asian & African-American donors





African-American



Asian

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Conclusions

- High prevalence of ferritin < 12 and < 26 confirmed
- Principal risk factors of age, sex, donation frequency confirmed
  - Sharp increase in risk for ID with increasing donation intensity
  - Large decrement in risk in females after age 50
- Secondary demographic and behavioral risk factors identified
  - Prevalence of ferritin <12 or < 26 is not equivalent by race in adjusted models
  - Daily iron supplementation appears superior to less than daily use
  - Use of antacid medications appears to increase risk by 20%
  - Use of exogenous hormones are associated with lower risk in females and higher risk in males
- Opportunity to refine donor management procedures with more personalized strategies