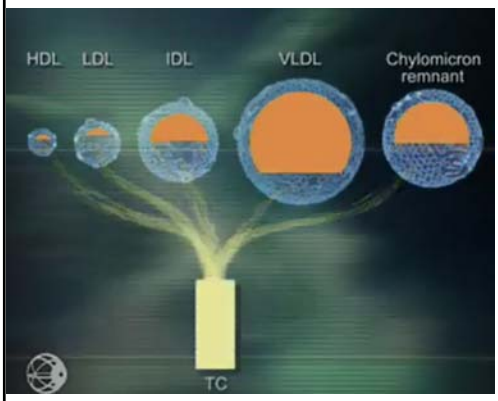
HDL Sub-fractions and CVD Morbidity/Mortality in African Americans

Associations of HDL Subclasses and Incident Cardiovascular Events in African Americans from the Jackson Heart Study

Michael E Griswold, PhD
Dir for Data Analytics, Jackson Heart Study
Professor & Director, Center of Biostatistics & Bioinformatics, UMMC

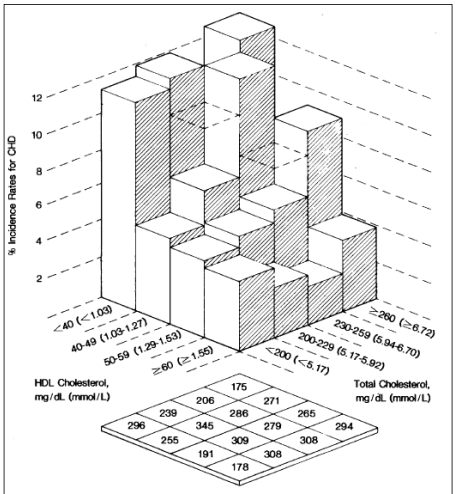
presenting on behalf of Parag Joshi, MD, Seth Lirette, MS, Seth Martin, MD, Michael Blaha, MD, MPH, Krishnaji Kulkarni, PhD, Adolfo Correa, MD, PhD, Herman Taylor, MD, and Steven Jones, MD for the Lipoprotein Investigators Collaborative (LIC)

Background: Cholesterol and CVD



- Guidelines have moved from measuring just TC *to* TC+TG *to* LDLc+HDLc+TG

If you wish to make an apple pie truly from scratch, you must first invent the universe. ~Carl Sagan



Castelli WP, Garrison RJ, Wilson PWF, et al. *JAMA* 1986;256:2835-2838.

Note: Please don't ever make a 3D BarChart

Background:

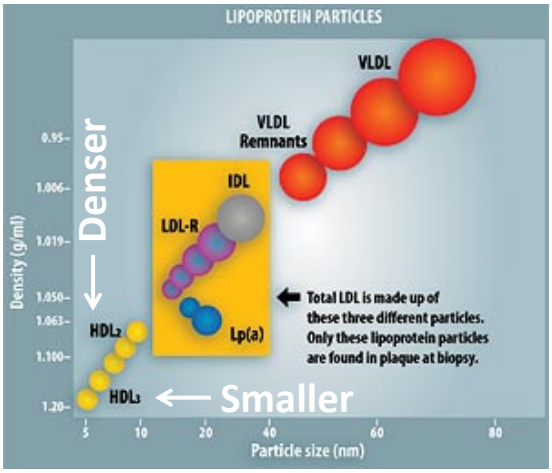
VLDL subcomponents

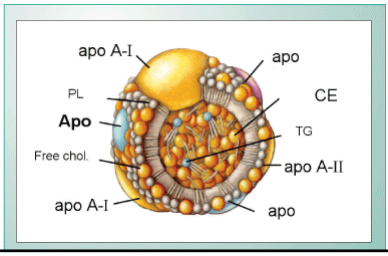
LDL subcomponents

HDL subcomponents

Hydrated Densities:

- VLDL: ~<1.006 g/ml
- LDL: ~1.006-1.063 g/ml
- HDL: ~1.063-1.21 g/ml
  - HDL2: 1.063-1.125 g/ml
  - HDL3: 1.125-1.21 g/ml





- Size + Composition:
  - Apo (A-I, A-II, B), ….
- A more sophisticated understanding of lipoproteins has been pursued…

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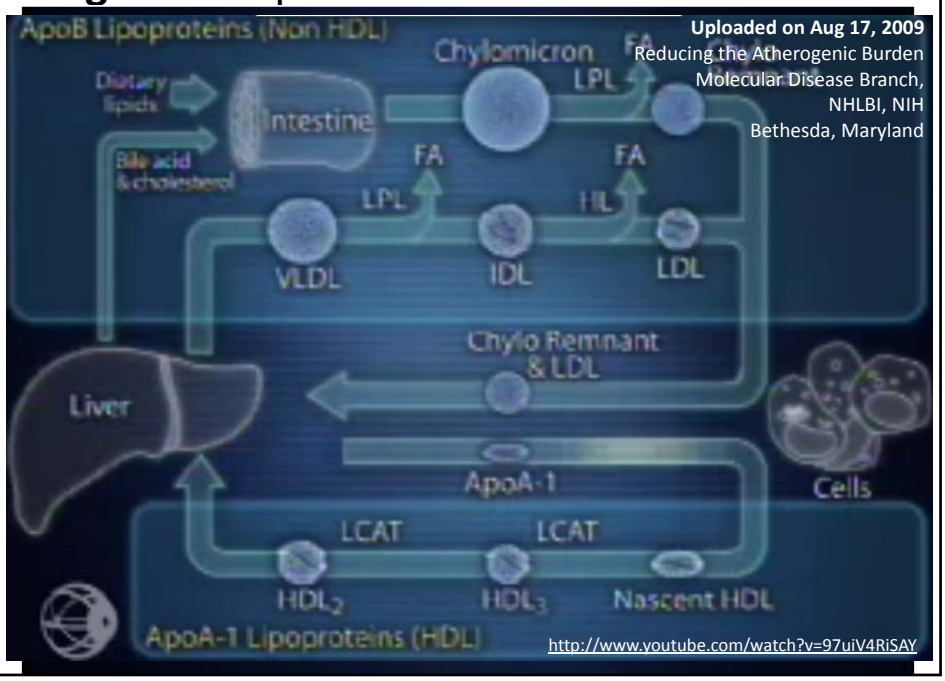
Background: apoA-I -> HDL3 -> HDL2 -> …



Background: Mixed Results

"Large Buoyant" (HDL_2-c) versus "Small Dense" (HDL_3-c)

- Nice Review:
  Superko (2012), *High Density Lipoprotein subclasses and their relationship to Cardiovascular Disease,* J Clin Lipid (6) 496-523
- **37 Case-Control Studies**
  - N=53 comparisons
    - 41 (78%) Men only
  - 26% HDL2c, 11% HDL3c
  - 17% neither, 45% both
- **8 Prospective Studies**
  - 1 HDL2c, 3 HDL3c, 4 both
- **Trials**: AIMHIGH & ILLUMINATE (↑HDL2)
  - Terminated early (eff/safety)

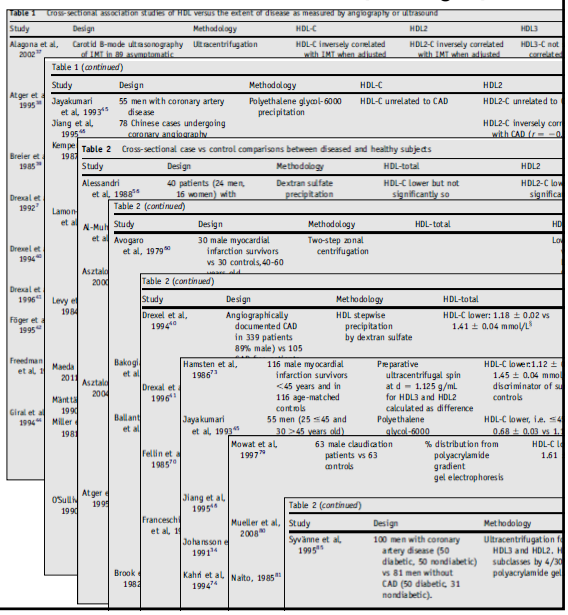


Table 1 Cross-sectional association studies of HDL versus the extent of disease as measured by angiography or ultrasound

Study	Design	Methodology	HDL-C	HDL2	HDL3
Alagona et al, 2002[57]	Carotid B-mode ultrasonography of IMT in 80 asymptomatic	Ultracentrifugation	HDL-C inversely correlated with IMT when adjusted	HDL2-C inversely correlated with IMT when adjusted	HDL3-C not correlated

Table 1 (*continued*)

Study	Design	Methodology	HDL-C	HDL2
Jayakumari et al, 1993[45]	55 men with coronary artery disease	Polyethalene glycol-6000 precipitation	HDL-C unrelated to CAD	HDL2-C unrelated to
Jiang et al, 1995[58]	78 Chinese cases undergoing coronary angiography			HDL2-C inversely cor with CAD ($r = -0$

Table 2 Cross-sectional case vs control comparisons between diseased and healthy subjects

Study	Design	Methodology	HDL-total	HDL2
Alessandri et al, 1988[56]	40 patients (24 men, 16 women) with	Dextran sulfate precipitation	HDL-C lower but not significantly so	HDL2-C low significa

Table 2 (*continued*)

Study	Design	Methodology	HDL-total	HD
Avogaro et al, 1979[60]	30 male myocardial infarction survivors vs 30 controls, 40-60	Two-step zonal centrifugation		Lo

Table 2 (*continued*)

Study	Design	Methodology	HDL-total
Drexel et al, 1994[40]	Angiographically documented CAD in 339 patients 89% male) vs 105	HDL stepwise precipitation by dextran sulfate	HDL-C lower: 1.18 ± 0.02 vs 1.41 ± 0.04 mmol/L[5]

Hamsten et al, 1986[73]	116 male myocardial infarction survivors <45 years and in 116 age-matched controls	Preparative ultracentrifugal spin at d = 1.125 g/mL for HDL3 and HDL2 calculated as difference	HDL-C lower:1.12 ± 1.45 ± 0.04 mmo discriminator of su controls	
Drexel et al, 1996[61]				
Jayakumari et al, 1993[45]	55 men (25 ≤45 and 30 >45 years old)	Polyethalene glycol-6000	HDL-C lower, i.e. ≤4 0.68 ± 0.03 vs 1.	
Mowat et al, 1997[74]	63 male claudication patients vs 63 controls	% distribution from polyacrylamide gradient gel electrophoresis	HDL-C (c 1.61	
Jiang et al, 1995[58]				
Mueller et al, 2008[80]				
Johansson et al, 1991[24]				
Kahri et al, 1994[26]				
Naito, 1985[81]				

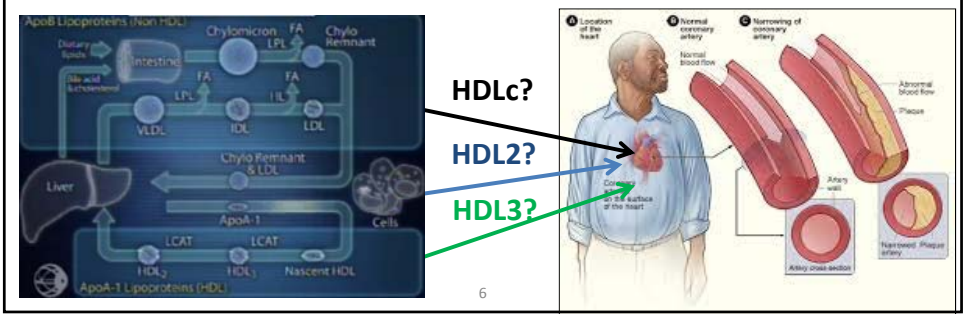
Table 2 (*continued*)

Study	Design	Methodology
Syvänne et al, 1995[65]	100 men with coronary artery disease (50 diabetic, 50 nondiabetic) vs 81 men without CAD (50 diabetic, 31 nondiabetic).	Ultracentrifugation f HDL3 and HDL2. H subclasses by 4/30 polyacrylamide ge

Background:

AIM

To examine **HDLc & HDLc-subclass** *(HDL2c, HDL3c)* relationships with **incident cardiovascular events** *(CHD, Fatal CHD, MI, Int. Cardiac Procs)* in **African Americans** from the **Jackson Heart Study**, while accounting for differential content markers (apo's).



Methods:

The Jackson Heart Study

- **Study**: Prospective, population-based, observational study of **5,301 African Americans** aged 20-84 from Jackson, MS; up to 8 years of F/U from 2000 to 2008 (median: ~5 yrs)
- **Outcomes**: Coronary Heart Disease (**CHD**) events including Fatal CHD, Myocardial Infarction (MI), Revascularizations
- **Lipoprotein measures**: Cholesterol subfractions by **density gradient ultracentrifugation** (**VAP test**, Atherotech, Birmingham, AL); Apolipoprotein A1 and B (**Abbott** Diagnostics, Lake Forest, IL). N= 4,722 markers measured from Exam 1 (baseline).
- **Analyses**: Cox PHM and logistic regression examining HDL subclasses and CHD; adjusted for combinations of:
  - age, sex, BMI, education, alcohol, smoking, SBP, DBP, lipid-altering medications, and apolipoproteins (ApoA-1, ApoB)

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Results:

**144 CHD events: 27 CHD deaths; 78 MIs; 39 revascularizations*

Baseline Characteristics

Variable		No CHD (n=4,578)	CHD* (n=144)	p-value
Gender, Female		64%	60%	0.29
Diabetes		17%	43%	<0.001
Education	< High School	17%	29%	<0.001
	High School/GED	42%	44%	
	College	41%	27%	
Smoking Status	Never	69%	56%	<0.001
	Former	18%	31%	
	Current	13%	14%	
Alcohol Use		47%	37%	0.015
Age (years)		53.9 (12.8)	64.3 (9.8)	<0.001
Body Mass Index (kg/m^2)		31.8 (7.3)	30.3 (6.1)	0.015
Waist Circumference (cm)		100.6 (16.3)	101.8 (13.7)	0.37
Systolic Blood Pressure (mmHg)		126.5 (18.2)	134.4 (19.9)	<0.001
Diastolic Blood Pressure (mmHg)		79.1 (10.4)	76.9 (11.2)	0.015
Lipid-altering Medications		11%	23%	<0.001

Participants with CHD were sicker in general (careful with confounding)

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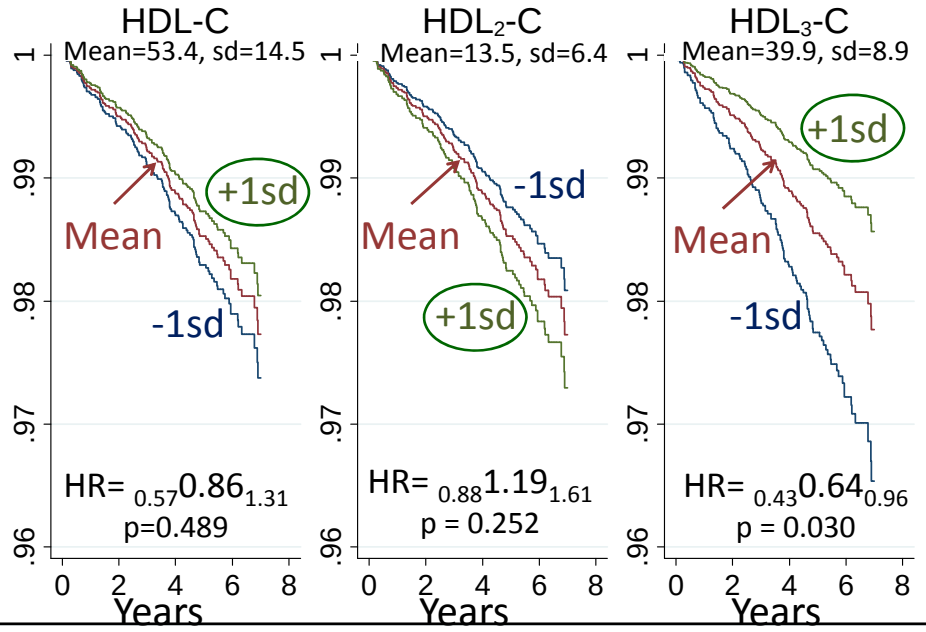
Results:

**Fully Adj. Models*

Predicted Survival: Standardized Cholesterol Classes



Results:

CHD Multivariable Survival Analyses across adjustment models

Model	HDL-C	HDL2-C	HDL3-C
Basic Adj: Age, Sex, BMI, Educ, Alcohol, Smoking, Blood Pressure, and lipid-meds	**0.79 (0.65,0.96) p=0.020**	0.88 (0.73,1.06) p=0.186	**0.76 (0.62,0.92) p=0.005**
Basic + ApoA-1	0.73 (0.50,1.06) p=0.099	1.00 (0.75,1.32) p=0.981	**0.60 (0.41,0.88) p=0.009**
Basic + ApoB	0.82 (0.67,1.00) p=0.055	0.92 (0.76,1.12) p=0.423	**0.78 (0.64,0.95) p=0.013**
Basic + ApoA-1 + ApoB	0.86 (0.57,1.31) p=0.489	1.19 (0.88,1.61) p=0.252	**0.64 (0.43,0.96) p=0.030**

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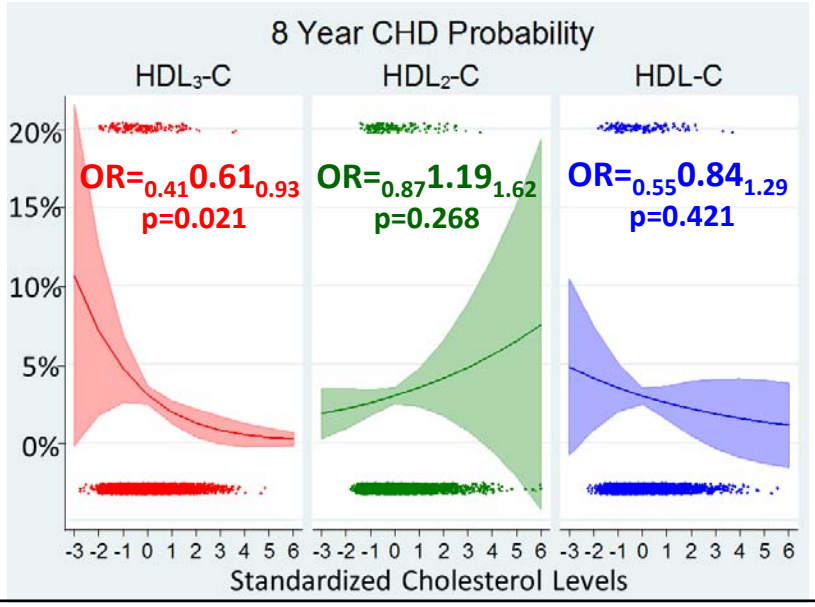
*Fully Adj. Models

Results:

HDL subclasses and 8-Year CHD events



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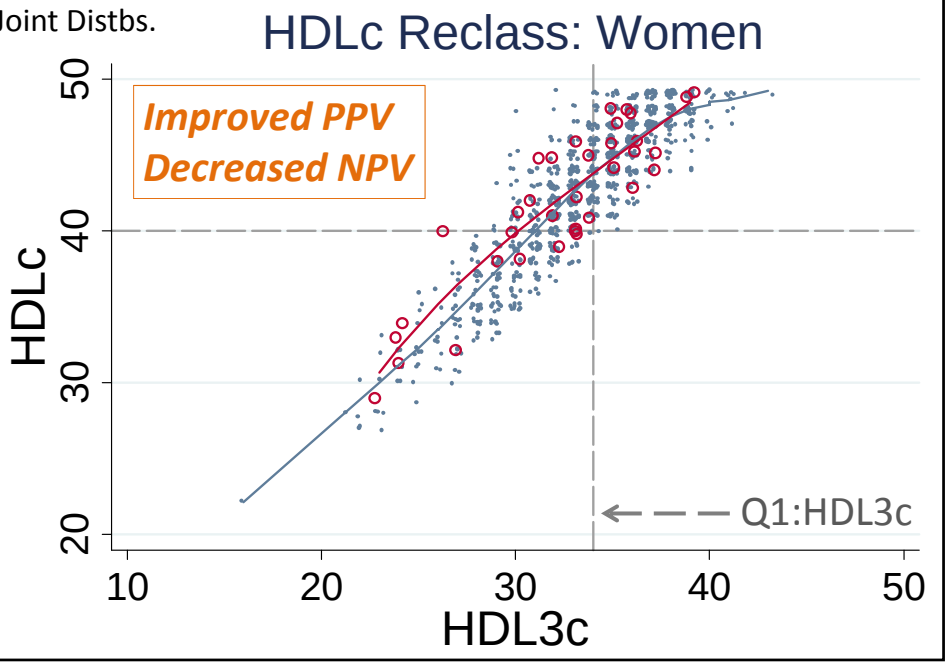
Results:

Shift in CHD joint distb (up & left) gives HDL3c some props

Joint Distbs.



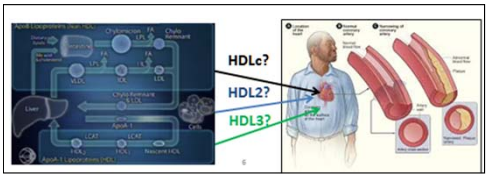
Risk Reclassification

Non-CHD Ptcpts		HDL3c Low Risk	HDL3c High Risk	Total
HDLc	Low Risk	3471	442	3913
		88.7	11.3	100
		75.82	9.65	85.47
	High Risk	2	663	665
		0.3	99.7	100
		0.04	14.48	14.53
	Total	3473	1105	4578
		75.86	24.14	100
		75.86	24.14	100

CHD Ptcpts		HDL3c Low Risk	HDL3c High Risk	Total
HDLc	Low Risk	91	24	115
		79.13	20.87	100
		63.19	**16.67**	79.86
	High Risk	0	29	29
		0	100	100
		0	20.14	20.14
N	Total	91	53	144
Row %		63.19	36.81	100
Cell %		63.19	36.81	100

***Note**: Be careful with Risk Reclassification statistics & interpretations. (NRI, IDI, etc.)*

Discussion: Strengths/Limitations



- Strengths:
  - **Largest study** of HDLc subclasses in African Americans and cardiovascular risk to our knowledge
  - **Robust adjustment** including apolipoproteins (as opposed to total and LDL cholesterol and TGs)
- Limitations:
  - Cross-sectional measurements do not reflect accumulated or time-varying exposures
  - HDLc (and subclasses) may be poor surrogates for true HDL
  - Singular geographic location and ethnic group
  - Younger Participant Base (lower event numbers)
  - HDL functionality within these subclasses is to be determined, though this is an important step in better understanding of the HDL structure-function relationship

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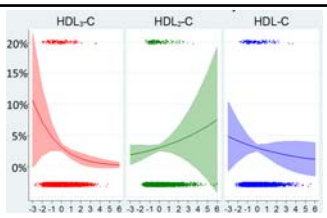
Discussion:
Interpretations & Implications



- Interpretations:
  - **HDL3c** appeared to drive relationships between overall HDLc and CHD endpoints in this sample of African Americans
- Implications:
  - Lipid and Lipoprotien **Subclasses** may offer increased risk stratification and early warning opportunities in similar African American populations, but too early now
- Future work:
  - Longitudinal Data and Risk Reclassification Modeling
  - LIC Consortium

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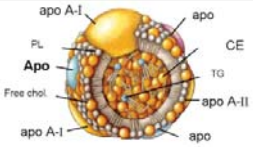
Acknowledgements



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  - Jackson Heart Study: Mike Griswold, Seth Lirette, Adolfo Correa, Herman Taylor
  - Oxford University: Arif Khokhar
  - University of Illinois: Peter Toth
  - Boston University: Ralph D'Agostino, Joseph Massaro
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  - Intermountain Medical Center: Heidi May, Brent Muhlestein, Jeffrey L. Anderson

- Our heartfelt thanks to all of the patients, providers, and staff who have worked to create and maintain this robust database

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In Review:
Things often can look similar but can have important differences…

Gavin & Connor Griswold

Thanks!
Questions?