Bayesian Hierarchical Model for Subgroup Analysis

Yun Wang
DBII/OB/OTS/CDER/FDA

Disclaimer

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Outline

- Background
- Bayesian hierarchical model (BHM) for one factor
- BHM for multiple factors
- Summary

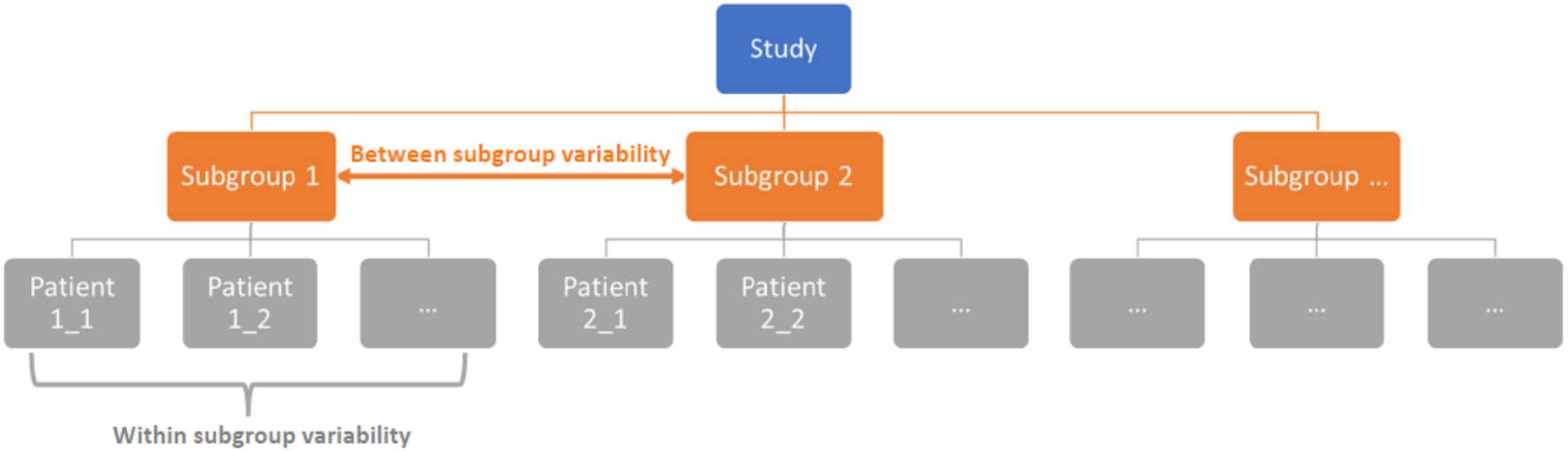
Outline

- Background
- Bayesian hierarchical model (BHM) for one factor
- BHM for multiple factors
- Summary

Exploratory Subgroup Analysis

- Not for efficacy claim in a specific subgroup
- Provide information on treatment effect in subgroups
  - Is there consistency in treatment effect?
  - What treatment effect can an individual patient expect?

Multi-level Variabilities in the Data



Sample Estimate

- Obtain a sample estimate of treatment effect for each subgroup separately
- Heterogeneous treatment effect (HTE)
- High variability in the estimated treatment effect

Symposiums and Workshops co-sponsored by FDA on HTE

- Nov 28, 2018, Symposium of Assessing and Communicating Heterogeneity of Treatment Effects for Patient Subpopulations: Challenges and Opportunities
  - Agenda, Slides and Recording at https://www.jhsph.edu/research/centers-and-institutes/center-of-excellence-in-regulatory-science-and-innovation/news-and-events/Critical-Issues-in-Heterogeneity-of-Treatment-Effect.html

- Nov 30 - Dec 1, 2020, Workshop on Heterogeneity of Treatment Effects in Clinical Trials: Methods and Innovations
  - Agenda and Recording at https://mrctcenter.org/news-events/heterogeneity-of-treatment-effects-in-clinical-trials-methods-and-innovations/#1602863324215-1289c9d5-a82a

Impact Story

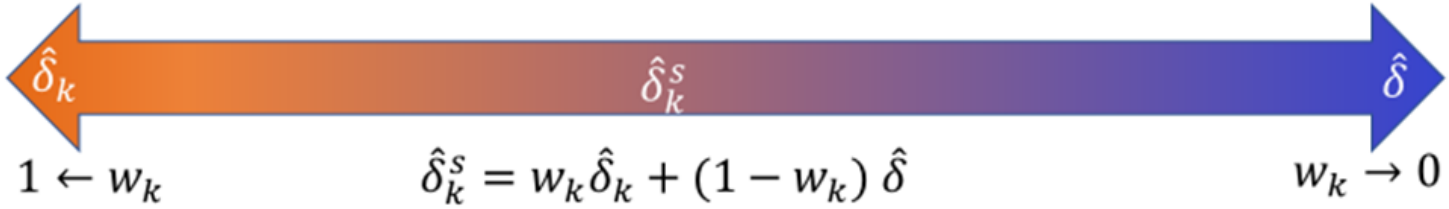
FDA Impact Story (2019). Using innovative statistical approaches to provide the most reliable treatment outcomes information to patients and clinicians. Available at:

[using-innovative-statistical-approaches-provide-most-reliable-treatment-outcomes]

Shrinkage Estimate

- Weighted average of sample estimates for subgroups and overall estimate.
  - Sample estimates are “shrunk” towards the overall estimate
  - Extent of shrinkage depends on ratio of within vs. between subgroup variability
- Less random high and low, more precise estimate

Illustration of Shrinkage



Weights/shrinkage depends on the ratio of the within-subgroup variability (σ_k^2) to the between-subgroup variability (τ^2),

$$w_k = \frac{\tau^2}{\sigma_k^2 + \tau^2}$$

Bayesian Hierarchical model (BHM)

- BHM to derive shrinkage estimate
  - Exchangeability in residual treatment effects
  - One factor or multiple factors
  - Summary level statistics
  - Patient level data

Outline

- Background
- Bayesian hierarchical model (BHM) for one factor
- BHM for multiple factors
- Summary

Case Study

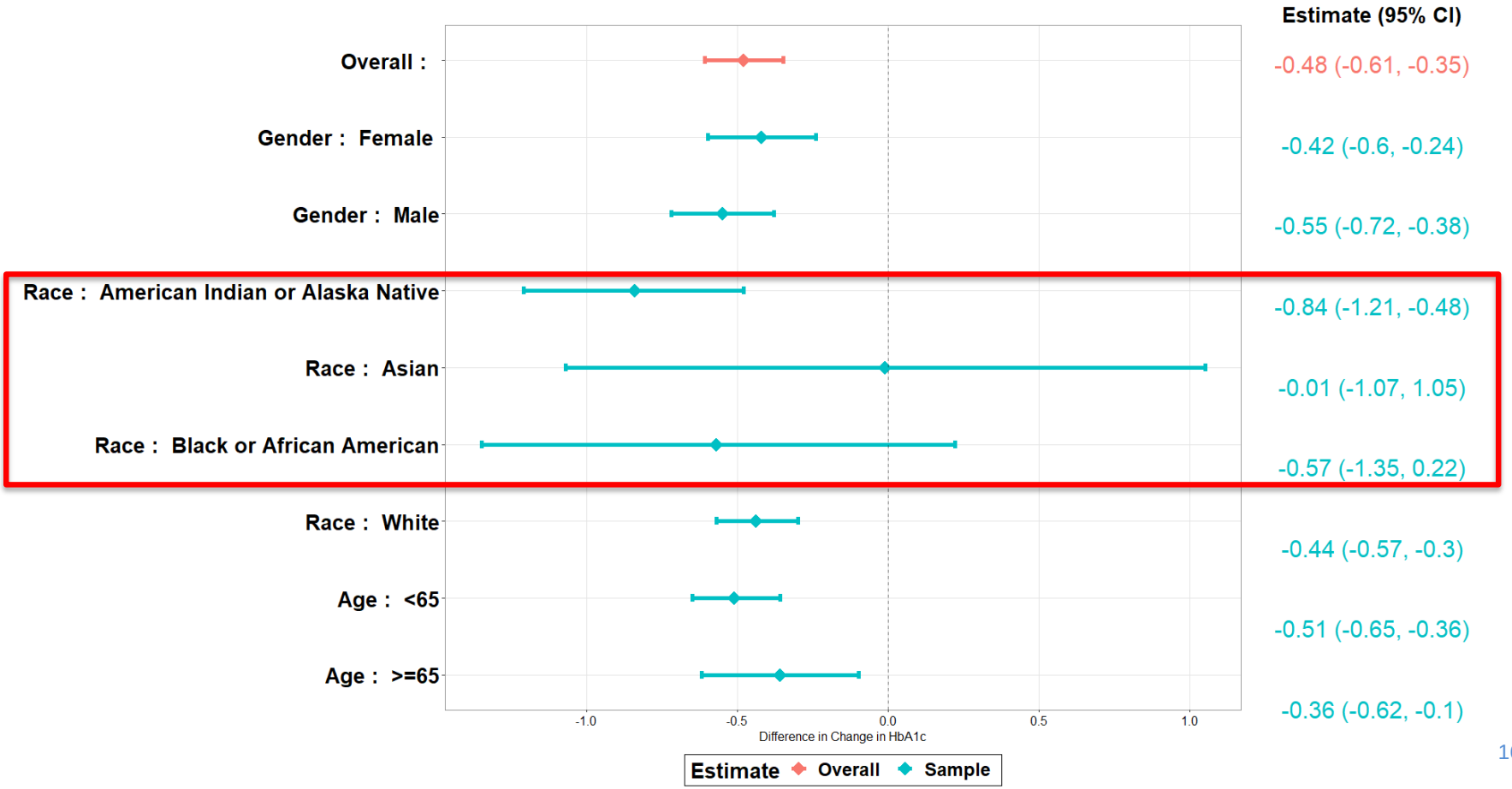
- MOUNJARO® (Tirzepatide) is a new molecular entity (NME) approved as adjunct to diet and exercise to improve glycemic control in patients with Type 2 diabetes mellitus (T2DM).
- Subgroup analysis were performed to estimate
  - Treatment effect by sex, race, and age subgroups
- SURPASS-2
  - Tirzepatide (5mg, 10mg, 15mg) vs. Semaglutide 1mg
  - Primary endpoint: change in HbA1c at Week 40 from baseline

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215866Orig1s000StatR.pdf

Case Study – Sample Estimates

	Mean Change in HbA1c (%) from Baseline				Difference in Mean Change (Tirzepatide - Semaglutide)
	Tirzepatide 15mg		Semaglutide 1mg		Sample Estimate (95% CI)
	N	Mean (SE)	N	Mean (SE)	
Overall	469	-2.33 (0.05)	468	-1.85 (0.05)	-0.48 (-0.61, -0.35)
Sex					
Female	256	-2.27 (0.06)	243	-1.85 (0.07)	-0.42 (-0.60, -0.24)
Male	213	-2.40 (0.06)	225	-1.84 (0.06)	-0.55 (-0.72, -0.38)
Race					
American Indian/Alaska Native	57	-2.73 (0.12)	45	-1.88 (0.14)	-0.84 (-1.21, -0.48)
Asian	5	-2.33 (0.35)	3	-2.32 (0.41)	-0.01 (-1.07, 1.05)
Black/ African American	15	-1.82 (0.27)	15	-1.25 (0.29)	-0.57 (-1.35, 0.22)
White	391	-2.30 (0.05)	400	-1.86 (0.05)	-0.44 (-0.57, -0.30)
Age					
< 65	366	-2.46 (0.05)	346	-1.95 (0.05)	-0.51 (-0.65, -0.36)
≥ 65	103	-1.91 (0.10)	122	-1.55 (0.09)	-0.36 (-0.62, -0.10)

Sample Estimates



Case Study – BHM Specifications (Summary Level)

Let $\hat{\delta}_k$ *(k = 1, ... K, K=2* for Sex and Age, *K=4* for Race*)* be the observed sample estimate of the treatment effect in subgroup *k*:

- $\hat{\delta}_k \sim N(\mu_k, \sigma_k^2)$,
  - μ_k is the expected treatment effect for subgroup *k*,
  - σ_k^2 is the within-subgroup variance, which is set to the observed variance for sample estimate
- $\mu_k \sim N(\mu, \tau^2)$
  - $\mu \sim N(0, (5)^2)$, a standard deviation of 5 , which was approximately five times the observed subject-level standard deviation of 1.
  - $\tau \sim$ *Half-Normal (0.5)*

Summary Level Statistics for BHM

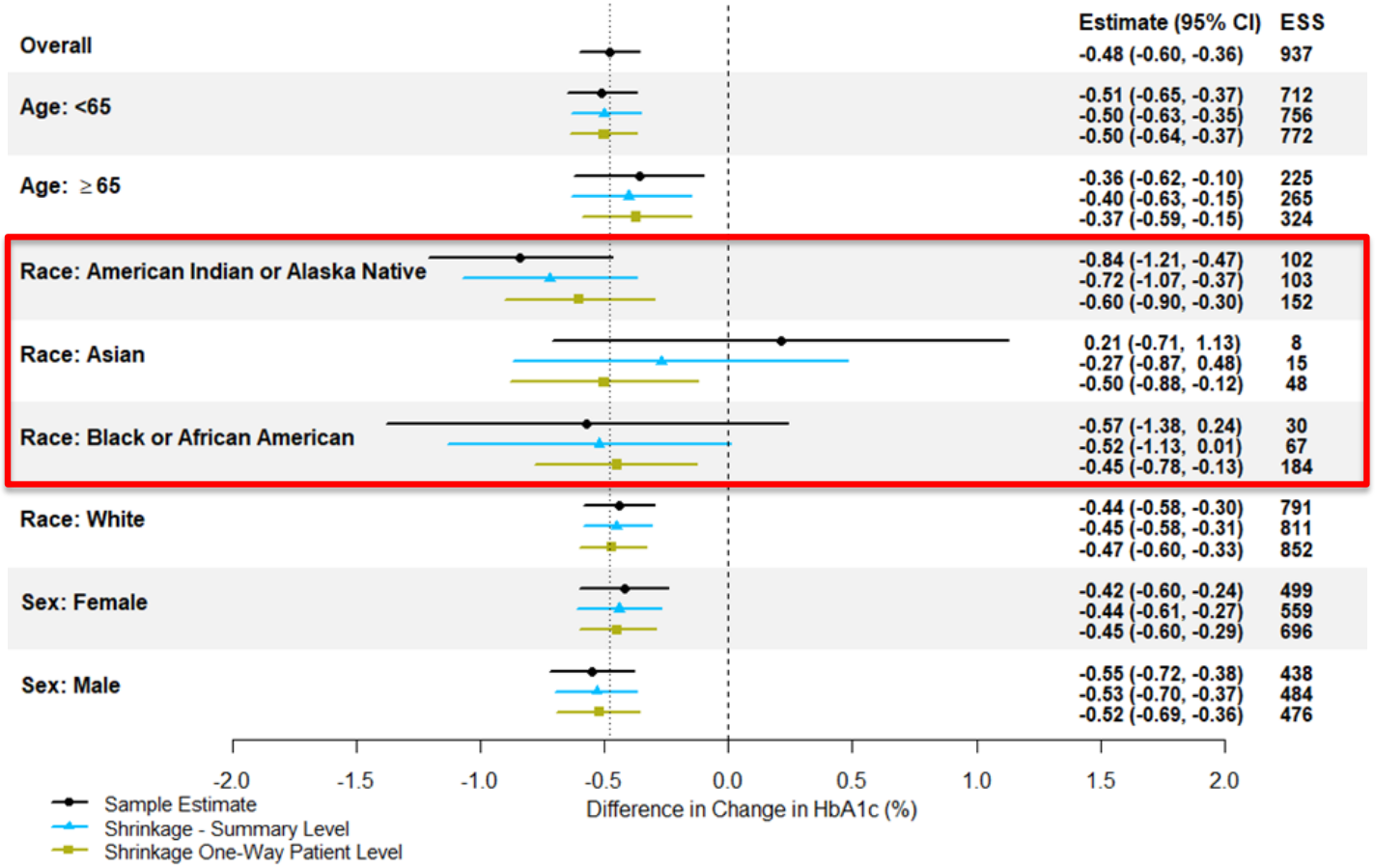
- Mean for continuous endpoint
- Odds ratio for dichotomous endpoint
- Rate ratio for count endpoint
- Hazard ratio for time to event endpoint

Case Study – BHM Specifications (Patient Level)

Let $Y_{i,k}$ (i = 1, ... N, k=1,..,K, K=2 for Sex and Age, K=4 for Race) be the observed outcome for patient i in subgroup k

- $Y_{i,k} \sim N(\mu_{i,k}, \sigma^2)$
  - $\mu_{i,k}$ is the expected outcome for patient i in subgroup k,
  - σ^2 is the residual variance
- $\mu_{i,k} = \beta_{1,k} + \beta_{2,k} * I(trt_i = 2) + \beta_{3,k} * Base_i + \beta_{4,k} * Base_i * I(trt_i = 2)$
  - $Base_i$: $Baseline\ HbA1c\ for\ Patient\ i - mean\ baseline\ HbA1c$
  - $\beta_{s,k} \sim N(\mu_s, \tau_s^2)$, $s = 1,2,3,4$, $k = 1,2$ for sex and age, $k = 1,2,3,4$ for race
  - $\mu_s \sim N(0, 25)$, $s = 1,2,3,4$
  - $\sigma, \tau_s \sim Half\text{–}Normal(1)$, $s = 1,2,3,4$

Shrinkage Estimates (Summary and Patient Level)



Effective Sample Size (ESS)

To evaluate how much information is borrowed across subgroups, we derive effective sample size (ESS) for each subgroup after shrinkage analysis. The following formula is used to calculate ESS:

$$ESS = n_k * \frac{var(\mu_k | data\ from\ subgroup\ k, ignore\ information\ from\ other\ subgroups)}{var(\mu_k | data\ from\ subgroup\ k, borrow\ information\ from\ other\ subgroups)}$$

where n_k is the sample size and μ_k is treatment effect parameter in subgroup k.

Outline

- Background
- Bayesian hierarchical model (BHM) for one factor
- BHM for multiple factors
- Summary

Personalized Medicine

- Patient: Female, Asian, < 65 years old
- What treatment effect can I expect?

Case Study Revisited

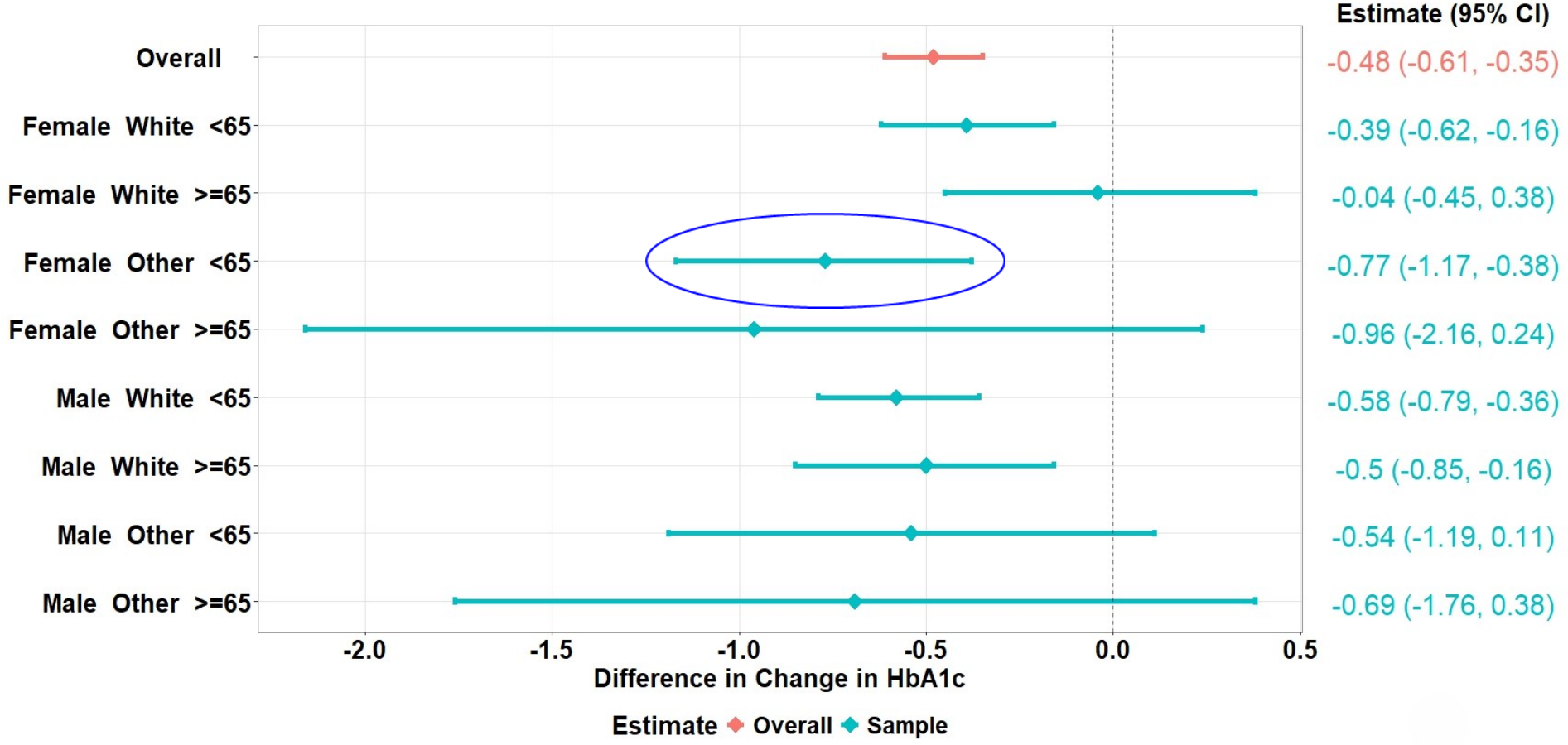
	Mean Change in HbA1c (%) from Baseline				Difference in Mean Change (Tirzepatide - Semaglutide)
	Tirzepatide 15mg		Semaglutide 1mg		Sample Estimate (95% CI)
	N	Mean (SE)	N	Mean (SE)	
Overall	469	-2.33 (0.05)	468	-1.85 (0.05)	-0.48 (-0.61, -0.35)
Sex					
Female	256	-2.27 (0.06)	243	-1.85 (0.07)	-0.42 (-0.60, -0.24)
Male	213	-2.40 (0.06)	225	-1.84 (0.06)	-0.55 (-0.72, -0.38)
Race					
American Indian/Alaska Native	57	-2.73 (0.12)	45	-1.88 (0.14)	-0.84 (-1.21, -0.48)
Asian	5	-2.33 (0.35)	3	-2.32 (0.41)	-0.01 (-1.07, 1.05)
Black/ African American	15	-1.82 (0.27)	15	-1.25 (0.29)	-0.57 (-1.35, 0.22)
White	391	-2.30 (0.05)	400	-1.86 (0.05)	-0.44 (-0.57, -0.30)
Age					
< 65	366	-2.46 (0.05)	346	-1.95 (0.05)	-0.51 (-0.65, -0.36)
≥ 65	103	-1.91 (0.10)	122	-1.55 (0.09)	-0.36 (-0.62, -0.10)

Case Study Revisited (Cont.)

			Mean Change in HbA1c from Baseline				Difference in Mean Change
			MOUNJARO 15mg		Semaglutide 1mg		Sample Estimate (95% CI)
			N	Mean (SE)	N	Mean (SE)	
Overall			469	-2.33 (0.05)	468	-1.85 (0.05)	-0.48 (-0.61, -0.35)
Sex	**Race**	**Age**					
Female	White	< 65	158	-2.40 (0.08)	154	-2.01 (0.08)	-0.39 (-0.62, -0.16)
		≥ 65	44	-1.51 (0.16)	51	-1.47 (0.15)	-0.04 (-0.45, 0.38)
	Other*	< 65	46	-2.58 (0.12)	30	-1.81 (0.16)	-0.77 (-1.17, -0.38)
		≥ 65	8	-2.40 (0.42)	8	-1.44 (0.42)	-0.96 (-2.16, 0.24)
Male	White	< 65	145	-2.48 (0.08)	141	-1.91 (0.08)	-0.58 (-0.79, -0.36)
		≥ 65	44	-2.14 (0.13)	54	-1.64 (0.12)	-0.50 (-0.85, -0.16)
	Other	< 65	17	-2.49 (0.25)	21	-1.95 (0.21)	-0.54 (-1.19, 0.11)
		≥ 65	7	-2.29 (0.42)	9	-1.60 (0.34)	-0.69 (-1.76, 0.38)

*Race Other include American Indian/Alaska Native, Asian, Black/ African American

One-way Sample Estimates



One-Way BHM Specifications (Summary Level)

Let $\hat{\delta}_k$ $(k = 1, \ldots 8)$ be the observed sample estimate of the treatment effect in subgroup k, *assume*:

- $\hat{\delta}_k \sim N(\mu_k, \sigma_k^2)$,
  - μ_k is the expected treatment effect for subgroup k,
  - σ_k^2 is the within-subgroup variance
- σ_k^2 is set to the observed variance for sample estimate
- $\mu_k \sim N(\mu, \tau^2)$
  - $\mu \sim N(0, 25)$
  - $\tau \sim$ *Half-Normal (1)*

One-Way BHM Specifications (Patient Level)

Let $Y_{i,k}$ ($i = 1, \ldots N$, $k=1,2,\ldots,8$) be the observed outcome for patient i in subgroup k, $Y_{i,k} \sim N(\mu_{i,k}, \sigma^2)$:

- $\mu_{i,k}$ is the expected outcome for patient i in subgroup k,
- σ^2 is the residual variance

$$\mu_{i,k} = \beta_{1,k} + \beta_{2,k} * I(trt_i = 2) + \beta_{3,k} * Base_i$$

$$\beta_{1,k} \sim N(\mu_1, \sigma_1^2), \quad \beta_{2,k} \sim N(\mu_2, \sigma_2^2), \beta_{3,k} \sim N(\mu_3, \sigma_3^2)$$

$$\mu_j \sim N(0, 25) \quad j = 1, 2, 3$$

$$\sigma, \sigma_j \sim Half - Normal(1) \quad j = 1, 2, 3$$

Multi-Way BHM Specifications (Patient Level)

Let $Y_{i,\,jklm}$ $(i = 1, \ldots N)$ be the observed outcome for patient i, in treatment group j, subgroup Sex_k, $Race_l$, and Age_m

$$Y_{i,\,jklm} \sim N\,(\mu_{i,\,jklm},\, \sigma^2)$$

- σ^2 is the residual variance
- $\mu_{i,\,jklm}$ is the expected outcome for patient i

$$= \sum_{u \in \{k,l,m\}} (\beta_{1,u} + \beta_{2,u} * I\,(j = 2) + \beta_{3,u} * X_i)$$

$$+ \sum_{v \in \{kl,km,lm\}} (\beta_{1,v} + \beta_{2,v} * I\,(j = 2) + \beta_{3,v} * X_i)$$

$$+ \beta_{1,klm} + \beta_{2,klm} * I(j = 2) + \beta_{3,klm} * X_i\ ,$$

Multi-way BHM Specifications (Patient Level Cont.)

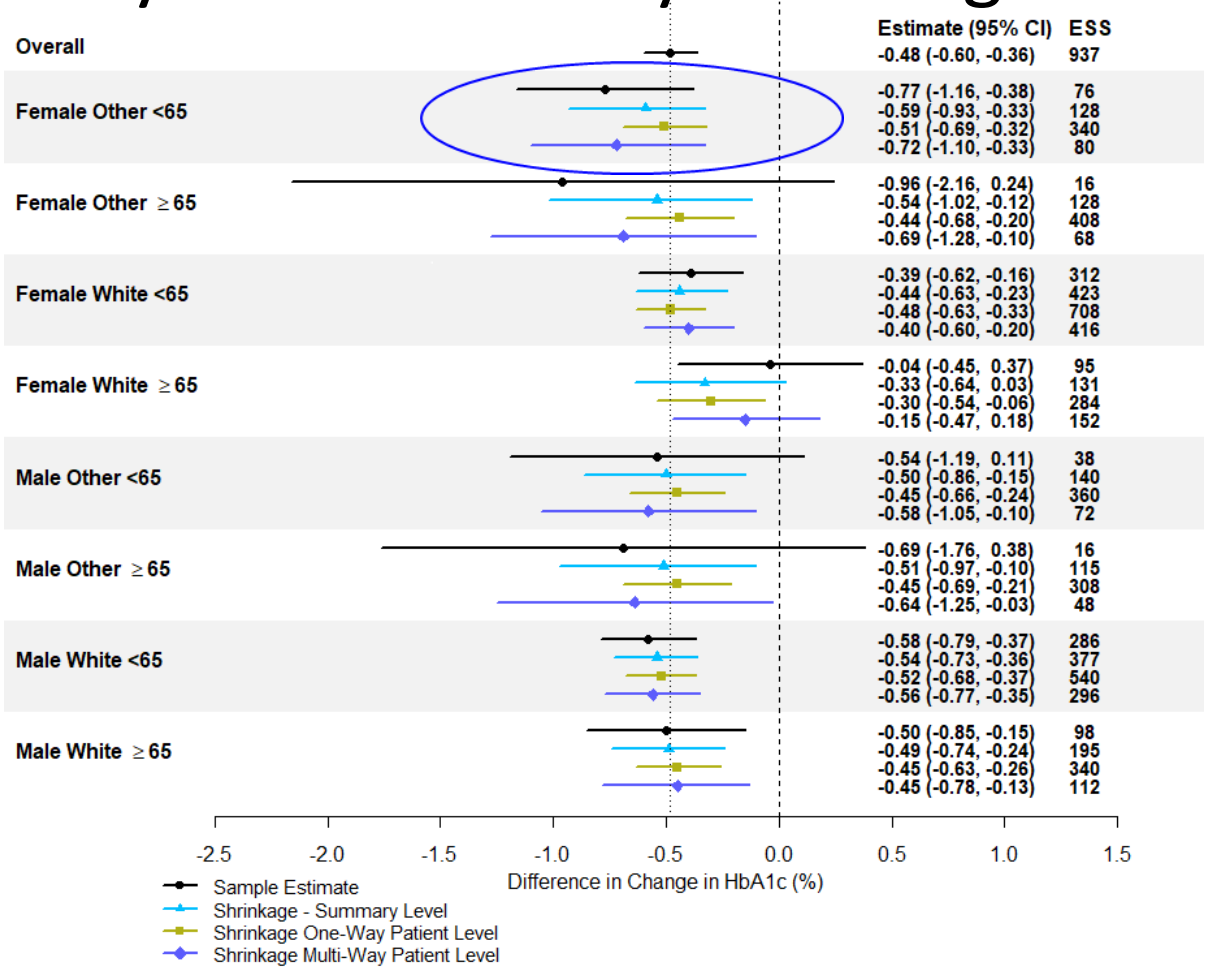
$\beta_{s,u}$, s = 1, 2, 3, and $u \in \{k, l, m\}$ represents the main effect for each factor; $\beta_{s,v}$, s = 1, 2, 3, and $v \in \{kl, km, lm\}$ represents the two-way interaction effect among factors; and $\beta_{s,klm}$, s = 1, 2, 3, represents the three-way interaction effect across all three factors.

$$\beta_{s,w} \sim N\left(\mu_{s,w}, \tau_{s,w}^2\right), \text{ s = 1, 2, 3, and } w \in \{k, l, m, kl, km, lm, klm\}$$

$$\mu_{s,w} \sim N(0, 25)$$

$$\sigma, \tau_{s,w} \sim Half-Normal\ (1)$$

One-way and Multi-way Shrinkage Estimates



Outline

- Background
- Bayesian hierarchical model (BHM) for one factor
- BHM for multiple factors
- Summary

Summary

- Bayesian hierarchical model provides more accurate estimate for subgroup treatment effect.
- Shrinkage estimates should, or at least along with sample estimates, be presented.
- Shrinkage estimates based on summary level statistics are often similar to shrinkage estimates based on patient level data.
- Shrinkage estimates based on patient level data can be used when normality assumption does not hold for summary level statistics.
- When multiple factors are involved simultaneously, multi-way shrinkage analysis may be more appropriate.

Reference

- Wang, Y., Tu, W., Koh, W., Travis, J., Abugov, R., Hamilton, K., Zheng, M., Crackel, R., Bonangelino, P. and Rothmann, M. (2024), Bayesian Hierarchical Models for Subgroup Analysis. Pharmaceutical Statistics. https://doi.org/10.1002/pst.2424
- Pennello G., Rothmann M., Bayesian Subgroup Analysis with Hierarchical Models, in Biopharmaceutical Applied Statistics Symposium Volume 2: Biostatistical Analysis of Clinical Trials, Eds. Karl E. Peace, Ding-Geng Chen, Sandeep Menon, Springer
- https://www.jhsph.edu/research/centers-and-institutes/center-of-excellence-in-regulatory-science-and-innovation/news-and-events/Critical-Issues-in-Heterogeneity-of-Treatment-Effect.html
- https://mrctcenter.org/news-events/heterogeneity-of-treatment-effects-in-clinical-trials-methods-and-innovations/#1602863324215-1289c9d5-a82a
- https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/212295Orig1s000StatR.pdf
- https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots-byfavo
- https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215866Orig1s000StatR.pdf
- IMPACT Story: using-innovative-statistical-approaches-provide-most-reliable-treatment-outcomes
- https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots

Acknowledgements

- Wenda Tu
- William Koh
- James Travis
- Robert Abugov
- Kiya Hamilton
- Mengjie Zheng
- Roberto Crackel
- Pablo Bonangelino
- Mark Rothmann


FDA
U.S. FOOD & DRUG
ADMINISTRATION