Racial and smoking status disparities in mediation effects on liraglutide-associated cardiovascular outcomes: a dynamic path analysis using LEADER trial data

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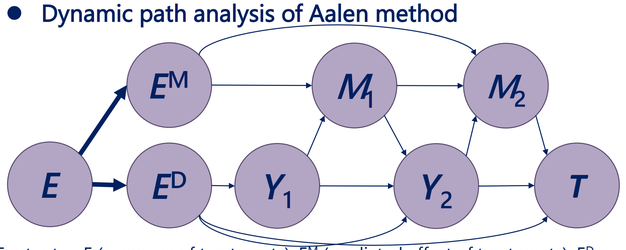
Background

- Mediation analyses are useful to disentangle possible causal pathways from an exposure/treatment to its clinically relevant outcomes.
- Mediation effects are commonly presented in changes in hazard ratios obtained from Cox proportional hazard model analyses, yet the assumption of proportionality is however violated with a post-exposure mediator added into the analysis.
- Dynamic path analysis of Aalen method



Footnotes: E (exposure of treatments); E^M (mediated effect of treatments); E^D (direct effect of treatments); M (mediators); Y (survival at different time points); T (outcomes of interest).

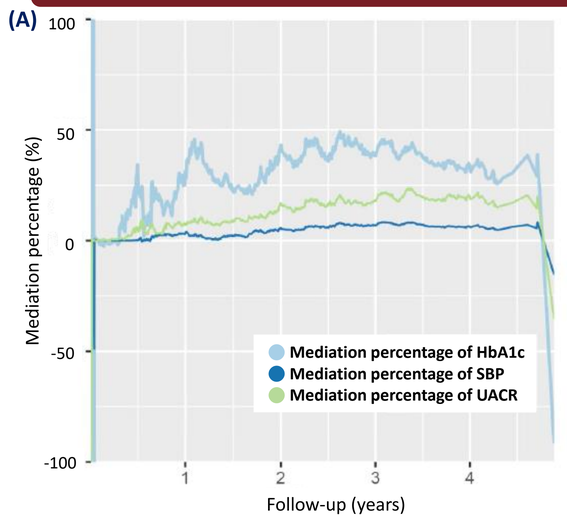
Objective

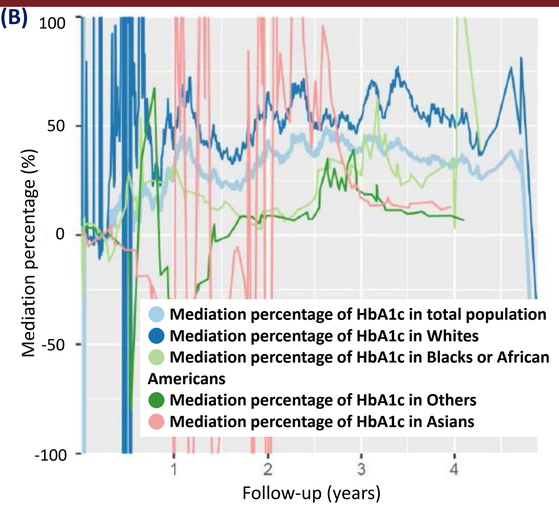
To apply dynamic path analyses for assessing the **heterogeneity of mediation effects** on liraglutide-associated major adverse cardiovascular event (MACE) outcome by **racial** and **smoking status** of patients.

Methods

- **Data source**: LEADER trial
- **Mediators of interest**: glycated hemoglobin (HbA1c), urine albumin-to-creatinine ratio (UACR), body weight (BW), systolic blood pressure (SBP), and low-density lipoprotein (LDL)
- **Mediation analysis**: Mediation percentage of treatment effect was estimated as mediated treatment effect divided by total treatment effect and corresponding bootstrap-based 95% confidence interval (CI) was generated.

Results





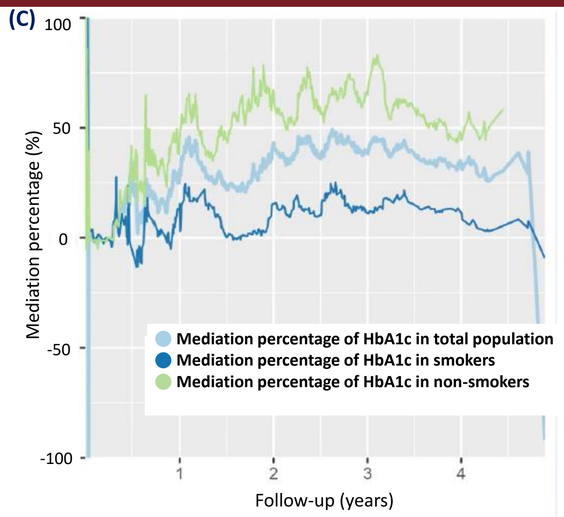


Figure (A). Mediation percentages of HbA1c, UACR, and SBP on MACE over 5 years
Figure (B). Heterogeneity in mediation effects of HbA1c for MACE outcome among different racial populations
Figure (C). Heterogeneity in mediation effects of HbA1c for MACE outcome among patients with different smoking status

(A)

Mediation percentage (95% CI)	
HbA1c	38.2% (11.9-286.7%)
UACR	17.9% (6.3-100.2%)
SBP	6.8% (2.6-33.2%)
BW	2.9% (-0.5-18.2%)
LDL	1.6% (-0.8-6.0%)

(B)

	Mediation percentage (95% CI)	
	HbA1c	UACR
Total population	38.2% (11.9-286.7%)	17.9% (6.3-100.2%)
Races		
Whites	53.9%	24.9%
Blacks or African Americans	27.4%	18.5%
Asians	18.7%	-0.46%
Others	17.4%	13.5%
Smoking status		
Smokers	64.8%	22.2%
Non-smokers	11.4%	8.5%

Table (A). Mediation effect of different clinical biomarkers on liraglutide-associated MACE outcome
Table (B). Heterogeneity in mediation effects of HbA1c and UACR on MACE among patient populations with different races and smoking status

Conclusions

- Significant mediators identified using dynamic path analyses are of clinical value and **consistent with previous findings**, thereby supporting the validity of dynamic path analyses in our illustration.
- Given the possibility of **disparities in HbA1c/UACR-mediated treatment effects** by **racial** and **smoking status**, further investigations on different causal pathways inherent to diverse patient clinical and behavioral characteristics are warranted in support of individualized medicine.

Acknowledgement

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