

# Effect of Glucagon on Risk of Ischemic Heart Disease: A Mendelian Randomization Study

Jack C M NG

School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China

## BACKGROUND INFORMATION

- Glucagon** is a peptide hormone derived from proglucagon, a protein encoded by *GCG* gene. Its main function is to stimulate glucose production in liver, thus raising blood glucose levels. Within the glucagon-insulin cycle, glucagon acts reciprocally with insulin to regulate blood glucose. **Previous research on glucagon has focused mainly on diabetes pathophysiology and treatment.**<sup>1-4</sup> To date, no randomized control trial of glucagon on cardiovascular diseases has been performed. **Recent Mendelian randomization (MR) studies have shown that insulin causes ischemic heart disease (IHD).**<sup>5,6</sup> It is unclear if glucagon, the counteracting hormone of insulin, also play a role in IHD.

## PROJECT OBJECTIVE

- To investigate the effect of glucagon on IHD using a two-sample MR study.

## MATERIALS AND METHODS

- Single-nucleotide polymorphisms (SNPs) that predict glucagon were obtained from a protein genome-wide association study (GWAS) consisting of 3,301 individuals of European descent.<sup>7</sup> SNPs that predict IHD were obtained from a meta-analysis largely based on the UK Biobank “SOFT CAD” GWAS consisting of up to 76,014 cases and 264,785 controls mainly of European ancestry.<sup>8</sup>
- SNP-specific Wald estimates were computed as the ratio of SNP-to-outcome association to SNP-exposure association and meta-analyzed using inverse variance weighted method with random effects.
- Sensitivity analyses were performed by (1) using different MR methods, (2) excluding proxy SNPs with  $r^2 < 0.7$  with and without exclusion of potential confounder(s), and (3) using SNPs that predict glucagon at  $p < 5 \times 10^{-8}$ .

## ACKNOWLEDGMENT

I am grateful to Dr C Mary Schooling for her supervision.

## REFERENCES

- Adeva-Andany MM, et al. Metabolic effects of glucagon in humans. *J Clin Transl Endocrinol.* 2018;15:45-53.
- Hædersdal S, et al. The Role of Glucagon in the Pathophysiology and Treatment of Type 2 Diabetes. *Mayo Clin Proc.* 2018;93(2):217-239.
- Petersen KM, et al. Hemodynamic Effects of Glucagon: A Literature Review. *J Clin Endocrinol Metab.* 2018 May 1;103(5):1804-1812.
- Scott RV, Bloom SR. Problem or solution: The strange story of glucagon. *Peptides.* 2018;100:36-41.
- Tikkanen E, et al. Genetic support for the causal role of insulin in coronary heart disease. *Diabetologia.* 2016;59(11):2369-2377.
- Zhan Y, et al. Exploring the Causal Pathway From Telomere Length to Coronary Heart Disease: A Network Mendelian Randomization Study. *Circ Res.* 2017;121(3):214-219.
- Nelson CP, et al. Association analyses based on false discovery rate implicate new loci for coronary artery disease. *Nat Genet.* 2017;49(9):1385-1391.
- Sun BB, et al. Genomic atlas of the human plasma proteome. *Nature.* 2018;558(7708):73-79.

## RESULTS

- Twenty-four SNPs strongly ( $p < 5 \times 10^{-6}$ ) and independently ( $r^2 < 0.05$ ) associated with glucagon were used. One SNP was associated with a potential confounder (alcohol use) and was discarded in sensitivity analysis (rs281377;  $p = 3 \times 10^{-7}$ ).
- Glucagon was positively associated with IHD (Table).** Results were similar in sensitivity analyses.

## CONCLUSIONS

- Genetically predicted higher level of glucagon was associated with a higher IHD risk.**
- MR study is a more feasible way to address the research question. It represents the long-term effect of exposure in which randomized control trial is unable to provide. Weak instrument bias is possible in the current study. However, bias due to weak instrument is towards null in two-sample MR and we observed a positive association.
- The mechanism through which glucagon affects IHD still needs further clarification as a target of intervention.**

Selection of SNPs	No. of SNPs	Mendelian randomization method	Odds ratio	95% confidence interval	p-value	Cochran's Q statistic (p-value)	MR-Egger Intercept p-value	MR-Egger I <sup>2</sup> <sub>ex</sub>
• $p < 5 \times 10^{-6}$	24	IVW	1.03	1.0003, 1.05	0.048	17.30 (0.79)	-	-
		WM	1.04	1.001, 1.08	0.048	-	-	-
		MR-Egger	1.01	0.95, 1.08	0.69	17.12 (0.76)	0.67	56%
		MR-PRESSO*	1.03	1.003, 1.05	0.03	-	-	-
• $p < 5 \times 10^{-6}$ • Proxy SNPs with $r^2 \geq 0.7$	22	IVW	1.03	1.00001, 1.06	0.04995	17.03 (0.71)	-	-
		WM	1.04	0.9997, 1.08	0.052	-	-	-
		MR-Egger	1.01	0.95, 1.08	0.72	16.83 (0.66)	0.66	36%
		MR-PRESSO*	1.03	1.00001, 1.06	0.04995	17.03 (0.71)	-	-
• $p < 5 \times 10^{-6}$ • Proxy SNPs with $r^2 \geq 0.7$ • Excluding confounder	21	IVW	1.02	0.996, 1.05	0.10	15.38 (0.75)	-	-
		WM	1.04	0.998, 1.08	0.06	-	-	-
		MR-Egger	1.02	0.95, 1.10	0.53	15.38 (0.70)	0.97	39%
		MR-PRESSO*	1.02	0.998, 1.05	0.07	-	-	-
• $p < 5 \times 10^{-8}$	2	IVW†	1.09	1.03, 1.15	0.003	0.05 (0.83)	-	-

IVW: inverse variance weighted; MR: Mendelian randomization; MR-PRESSO: Mendelian randomization pleiotropy residual sum and outlier; SNP: single-nucleotide polymorphism; WM: weighted median.

\*No outlier was detected.  
†With fixed effects.

**Table.** Mendelian randomization associations of glucagon (based on 24 independent single-nucleotide polymorphisms) with ischemic heart disease.