SUPPLEMENTAL MATERIALS

Bidirectional Temporal Relationship between Obesity and Hyperinsulinemia:

Longitudinal Observation from a Chinese Cohort

Chao Xu [1,2,3*], Guangshuai Zhou [4,5*], Meng Zhao[1,2,3], Xu Zhang[1,2,3], Li Fang[1,2,3], Qingbo Guan[1,2,3], Haiqing Zhang[1,2,3], Ling Gao[2,3,6], Tao Zhang[4#], Jiajun Zhao [1,2,3#]

[1] Department of Endocrinology and Metabolism, Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong,250021, China;

[2] Institute of Endocrinology, Shandong Academy of Clinical Medicine, Jinan 250021, Shandong, China;

[3] Shandong Clinical Medical Center of Endocrinology and Metabolism, Jinan 250021, Shandong, China;

[4] Department of Biostatistics, School of Public Health, Cheeloo College of Medicine, Shandong University, 250012, Jinan, Shandong, China;

[5] Department of Quality Management Office, Zibo Central Hospital, Zibo 255036, Shandong, China

[6]Scientific Center, Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong,250021, China.

Running Title: Temporal Sequence between Obesity and insulin

The authors do not have any conflict of interest.

* These authors contributed equally.

#Correspondence & Reprints:

Jiajun Zhao, MD, PhD. Department of Endocrinology, Shandong Provincial Hospital affiliated to Shandong University, Jinan, Shandong, China.

Email: jjzhao@medmail.com.cn

Tao Zhang, MD, PhD, Department of Biostatistics, School of Public Health, Cheeloo College

of Medicine, Shandong University. PO Box 100, 44 Wenhuaxi Road, Jinan, 250012, China.

Email: taozhang@sdu.edu.cn

Supplement Table S1. Pearson Correlation Coefficients Between BMI and Insulin，HOMA-IR or HOMA-%β*.

Variable	Baseline BMI	Baseline Insulin	Baseline HOMA-IR	Baseline HOMA-%β	Follow-up BMI	Follow-up Insulin	Follow-up HOMA-IR
Baseline Insulin	0.444	…	…	…	…	…	…
Baseline HOMA-IR	0.441	0.998	…	…	…	…	…
Baseline HOMA-%β	0.391	0.828	0.790	…	…	…	…
Follow-up BMI	0.770	0.401	0.399	0.341	…	…	…
Follow-up Insulin	0.424	0.572	0.570	0.482	0.485	…	…
Follow-up HOMA-IR	0.424	0.567	0.567	0.462	0.483	0.998	…
Follow-up HOMA-%β	0.337	0.503	0.485	0.568	0.411	0.831	0.794

BMI indicates body mass index. Insulin HOMA-IR and HOMA-%β were log-transformed for normal distribution.

*Adjusted for age, sex, smoking, drinking and follow-up years. Correlation coefficients >0.065 are significant ($P<0.05$).

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Supplement Table S2. Pearson Correlation Coefficients Between WC and Insulin, HOMA-IR or HOMA-%β.

Variable	Baseline WC	Baseline Insulin	Baseline HOMA-IR	Baseline HOMA-%β	Follow-up WC	Follow-up Insulin	Follow-up HOMA-IR
Baseline Insulin	0.389	…	…	…	…	…	…
Baseline HOMA-IR	0.388	0.998	…	…	…	…	…
Baseline HOMA-%β	0.325	0.828	0.790	…	…		…
Follow-up WC	0.507	0.368	0.365	0.324	…	…	…
Follow-up Insulin	0.379	0.572	0.570	0.482	0.417	…	…
Follow-up HOMA-IR	0.378	0.567	0.567	0.462	0.418	0.998	…
Follow-up HOMA-%β	0.322	0.503	0.485	0.568	0.324	0.831	0.794

WC indicates waist circumference. Insulin HOMA-IR and HOMA-%β were log-transformed for normal distribution.

*Adjusted for age, sex, smoking, drinking and follow-up years. Correlation coefficients >0.065 are significant ($P<0.05$).

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Supplement Table S3. Pearson Correlation Coefficients Between HC and Insulin, HOMA-IR or HOMA-%β*.

Variable	Baseline HC	Baseline Insulin	Baseline HOMA-IR	Baseline HOMA-%β	Follow-up HC	Follow-up Insulin	Follow-up HOMA-IR
Baseline Insulin	0.314	…	…	…	…	…	…
Baseline HOMA-IR	0.312	0.998	…	…	…	…	…
Baseline HOMA-%β	0.269	0.828	0.790	…	…	…	
Follow-up HC	0.448	0.333	0.330	0.292	…	…	…
Follow-up Insulin	0.335	0.572	0.570	0.482	0.400	…	…
Follow-up HOMA-IR	0.328	0.567	0.567	0.462	0.399	0.998	…
Follow-up HOMA-%β	0.326	0.503	0.485	0.568	0.328	0.831	0.794

HC indicates hip circumference. Insulin HOMA-IR and HOMA-%β were log-transformed for normal distribution.

*Adjusted for age, sex, smoking, drinking and follow-up years. Correlation coefficients >0.065 are significant ($P<0.05$).

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Supplement Table S4. Pearson Correlation Coefficients Between WHR and Insulin , HOMA-IR or HOMA-%β.

Variable	Baseline WHR	Baseline Insulin	Baseline HOMA-IR	Baseline HOMA-%β	Follow-up WHR	Follow-up Insulin	Follow-up HOMA-IR
Baseline Insulin	0.195	…	…	…	…	…	…
Baseline HOMA-IR	0.196	0.998	…	…	…	…	…
Baseline HOMA-%β	0.152	0.828	0.790	…	…	…	…
Follow-up WHR	0.255	0.198	0.197	0.174	…	…	…
Follow-up Insulin	0.151	0.572	0.570	0.482	0.200	…	…
Follow-up HOMA-IR	0.157	0.567	0.567	0.462	0.202	0.998	…
Follow-up HOMA-%β	0.068	0.503	0.485	0.568	0.138	0.831	0.794

WHR indicates waist-to-hip ratio. Insulin HOMA-IR and HOMA-%β were log-transformed for normal distribution.

*Adjusted for age, sex, smoking, drinking and follow-up years. Correlation coefficients >0.065 are significant ($P<0.05$).

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Supplement Table S5. The cross-lagged path coefficients by sex, with adjustment for covariates.

	Men (n=860)		Women (n=1633)		Sex difference	
	β_1	β_2	β_1	β_2	*P* for β_1	*P* for β_2
BMI ↔ Insulin	0.072*	0.253*	0.075*	0.222*	0.943	0.436
WC ↔ Insulin	0.195*	0.233*	0.198*	0.159*	0.941	0.068
HC ↔ Insulin	0.232*	0.178*	0.194*	0.143*	0.345	0.394
WHR ↔ Insulin	0.167*	0.116*	0.148*	0.054*	0.644	0.139
BMI ↔ HOMA-IR	0.071*	0.254*	0.076*	0.225*	0.905	0.466
WC ↔ HOMA-IR	0.192*	0.231*	0.196*	0.161*	0.922	0.084
HC ↔ HOMA-IR	0.229*	0.176*	0.192*	0.142*	0.359	0.408
WHR ↔ HOMA-IR	0.166*	0.115*	0.146*	0.058*	0.627	0.173
BMI ↔ HOMA-%β	0.062*	0.207*	0.045*	0.153*	0.686	0.186
WC ↔ HOMA-%β	0.180*	0.233*	0.174*	0.119*	0.883	0.005
HC ↔ HOMA-%β	0.215*	0.184*	0.166*	0.130*	0.228	0.189
WHR ↔ HOMA-%β	0.140*	0.121*	0.139*	0.011	0.981	0.009

Covariates included age, smoking, drinking and follow-up years.

BMI indicates body mass index; WC, waist circumference; HC, hip circumference; WHR, waist to hip ratio; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-%β, homeostasis model assessment of beta cell function. Insulin

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HOMA-IR and HOMA-%β were log-transformed for normal distribution.

β_1 describes the cross-lagged path coefficient from baseline Insulin, HOMA-IR or HOMA-%β to follow-up BMI/WC/HC/WHR; β_2

describes the cross-lagged path coefficient from baseline BMI/WC/HC/WHR to follow-up Insulin, HOMA-IR or HOMA-%β.

*P <0.05 for β_1 and β_2 being different from 0.

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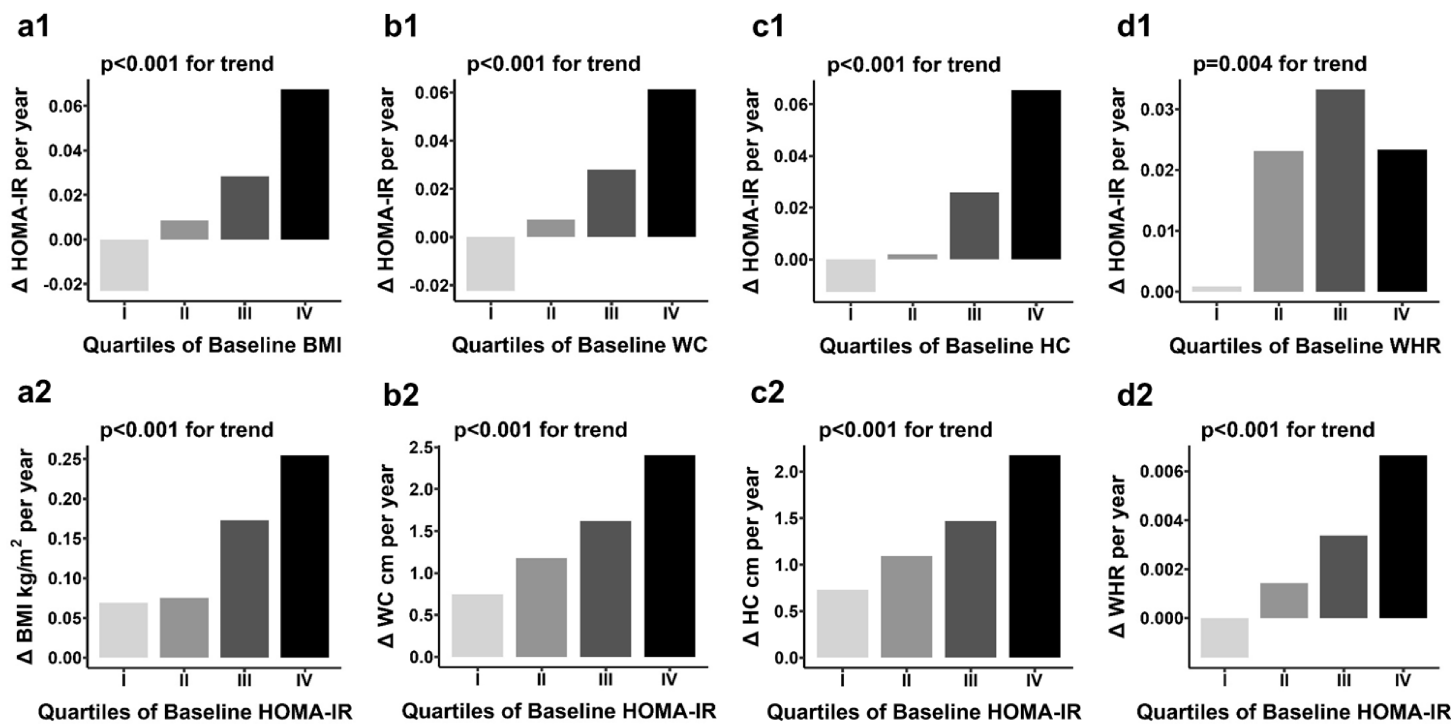
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Supplement Table S6. The cross-lagged path coefficients by excluding participants with pre-diabetes at baseline and follow-up

(N=1029)

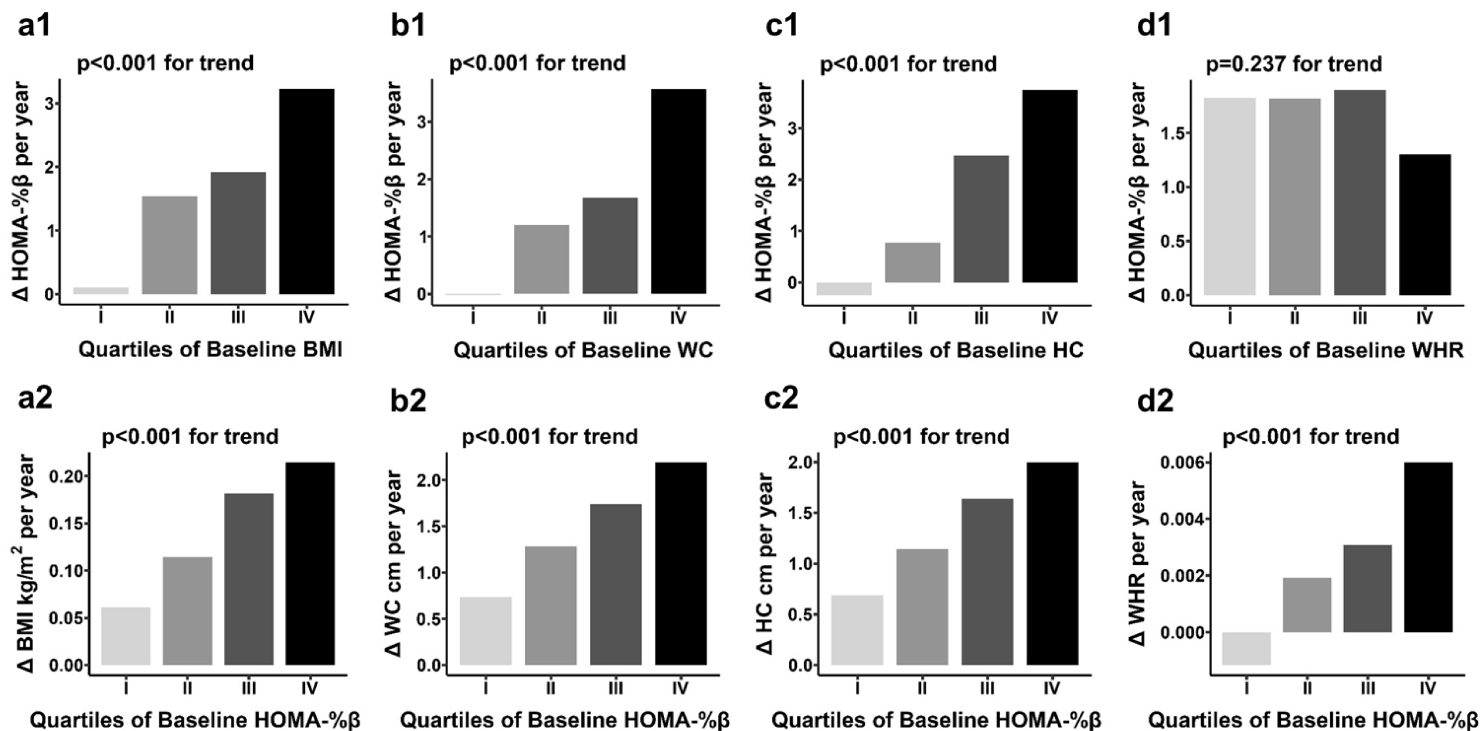| Obesity Measures	IR Measures	Path coefficients (IR → Obesity)			Path coefficients (Obesity → IR)		*P* value†	RMR	CFI
		β₁	95% CI		β₂	95% CI			
BMI	Insulin	0.057*	0.014~0.101		0.225*	0.171~0.279	<0.001	0.018	0.99
WC	Insulin	0.176*	0.118~0.233		0.203*	0.150~0.255	0.526	0.010	0.992
HC	Insulin	0.184*	0.127~0.242		0.163*	0.111~0.214	0.624	0.012	0.95
WHR	Insulin	0.121*	0.061~0.182		0.097*	0.046~0.148	0.582	0.024	0.854
BMI	HOMA-IR	0.058*	0.014~0.102		0.225*	0.171~0.280	<0.001	0.017	0.99
WC	HOMA-IR	0.171*	0.113~0.228		0.200*	0.147~0.253	0.496	0.009	0.993
HC	HOMA-IR	0.181*	0.123~0.238		0.160*	0.107~0.212	0.624	0.011	0.950
WHR	HOMA-IR	0.119*	0.059~0.180		0.098*	0.046~0.149	0.630	0.023	0.851
BMI	HOMA-%β	0.037	-0.006~0.079		0.194*	0.142~0.245	<0.001	0.024	0.988
WC	HOMA-%β	0.176*	0.120~0.231		0.202*	0.152~0.252	0.541	0.016	0.988
HC	HOMA-%β	0.174*	0.117~0.230		0.174*	0.125~0.224	1.000	0.017	0.947
WHR	HOMA-%β	0.113*	0.053~0.173		0.089*	0.040~0.139	0.583	0.033	0.852

Covariates included age, sex, smoking, drinking and follow-up years.

β₁ describes the cross-lagged path coefficient from baseline HOMA-IR or HOMA-%β to follow-up BMI/WC/HC/WHR; β₂

describes the cross-lagged path coefficient from baseline BMI/WC/HC/WHR to follow-up HOMA-IR or HOMA-%β.

*$P<0.05$ for β₁ and β₂ being different from 0; †P value for difference between β₁ and β₂.

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Supplement Figure S1. Yearly rates of change (Δ) of obesity measures and HOMA-IR by quartiles of their baseline values in the total sample, with adjustment of age, sex, smoking, drinking and their baseline values.

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Supplement Figure S2. Yearly rates of change (Δ) of obesity measures and HOMA-%β by quartiles of their baseline values in

the total sample, with adjustment of age, sex, smoking, drinking and their baseline values.