

SUPPLEMENTARY DATA

Supplementary Table 1. Glipizide challenge: Comparison of glucose and insulin response in individuals with or without type 2 diabetes mellitus stratified by the *HNF1A* p.E508K status. Data are presented as mean \pm standard deviation (M \pm SD) or median and interquartile range. *p*-value for comparison between carriers and non-carriers.

Parameter	Without Type 2 diabetes			Type 2 diabetes		
	p.E508	p.E508K	p-value	p.E508	p.E508K	p-value
Minimum glucose peak	58.62 \pm 11.61	57.09 \pm 9.01	0.56	75.19 \pm 25.39	72.86 \pm 25.39	0.81
Glucose average	79.08 \pm 15.79	77.84 \pm 6.50	0.68	107.94 \pm 33.17	99.24 \pm 29.95	0.46
AOC Glucose	69.75 (50.37-109.12)	79.62 (55.69-108.75)	0.61	145.25 (116.0-168.81)	111.87 (99.00-149.81)	0.046
AUC Glucose	306.90 \pm 60.30	296.01 \pm 45.95	0.42	399.00 \pm 148.30	377.25 \pm 148.30	0.66
IAUC Glucose	74.26 \pm 65.63	67.05 \pm 45.08	0.41	144.11 \pm 75.04	131.48 \pm 75.04	0.09
Delta Glucose Final-Basal	-15.84 \pm 10.63	-16.71 \pm 9.51	0.73	-51.60 \pm 36.72	-38.21 \pm 36.72	0.22
Delta Glucose Min peak-Basal	-40.66 \pm 15.25	-38.66 \pm 11.46	0.55	-64.19 \pm 33.39	-52.50 \pm 33.39	0.23
Delta Glucose Min peak-Final	-24.81 \pm 14.48	-21.52 \pm 12.35	0.33	-13.93 \pm 14.23	-14.28 \pm 14.23	0.94
Maximum insulin peak	24.2 (12.2-42.1)	19.8 (14.8-32.2)	0.44	32.6 (19.1 – 47.0)	19.3 (10.8-25.9)	0.03
Insulin average	11.6 (6.6-20.1)	9.7 (7.0-11.4)	0.66	13.0 (7.0-25.4)	11.6 (6.1-16.3)	0.33
TAUC Insulin	43.2 (26.4-76.4)	37.9 (25.5-75.1)	0.77	49.4 (26.6-98.7)	45.2 (22.8-65.4)	0.29
IAUC Insulin	12.9 (4.8-27.5)	9.7 (4.5-22.7)	0.73	15.2 (10.3-29.9)	14.1 (8.5-22.7)	0.85
Delta Insulin Final-Basal	-0.75 (-2.6 – 0.57)	-0.4 (-2.1 – 1.2)	0.54	-3.6 (-7.5 - -1.3)	0.15 (-3.3 – 1.5)	0.047
Delta Insulin Max peak-Basal	16.3 (6.8-30.9)	12.3 (7.7-24.6)	0.56	22.5 (15.4 – 29.8)	10.8 (7.4 – 17.0)	0.03
Delta Insulin Max peak-Final	17.4 (7.3-29.5)	13.1 (7.4-24.4)	0.47	29.5 (15.4 – 29.8)	11.6 (8.3- 18.5)	0.01

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Supplementary Table 2. Comparison of glucose and insulin response in individuals with or without type 2 diabetes mellitus during the OGTT challenge under metformin stratified by the *HNF1A* p.E508K status. Data are presented as mean \pm standard deviation (M \pm SD) or median and interquartile range. *p*-value for comparison between carriers and non-carriers

Parameter	Without type 2 diabetes			Type 2 diabetes		
	p.E508	p.E508K	p-value	p.E508	p.E508K	p-value
Minimum glucose peak	94.41 \pm 13.78	91.03 \pm 10.89	0.28	127.20 \pm 46.85	135.64 \pm 46.85	0.68
Glucose average	126.67 \pm 27.45	118.14 \pm 22.19	0.18	190.97 \pm 50.46	176.48 \pm 50.46	0.48
Fasting glucose V2	97.12 \pm 7.62	91.91 \pm 7.61	0.01	125.85 \pm 13.39	126.23 \pm 13.89	0.94
TAUC Glucose	255.67 \pm 78.46	246.07 \pm 51.75	0.56	380.61 \pm 143.17	373.87 \pm 143.17	0.89
IAUC Glucose	-78.19 \pm 38.38	-86.98 \pm 46.47	0.61	-158.50 \pm 64.90	-124.18 \pm 64.90	0.65
Delta Glucose Final-Basal	23.94 \pm 32.09	30.56 \pm 39.88	0.45	83.67 \pm 49.97	78.14 \pm 49.97	0.82
Delta Glucose Min peak-Basal	-3.47 \pm 7.18	-0.62 \pm 8.83	0.16	-2.07 \pm 8.00	13.07 \pm 8.00	0.31
Delta Glucose Min peak-Final	-27.41 \pm 28.31	-31.19 \pm 36.85	0.65	-85.73 \pm 48.56	-65.07 \pm 48.56	0.34
Maximum insulin peak	64.0 (46.9-112.7)	53.3 (36.4 – 97.7)	0.26	63.9 (37.2 – 114.3)	32.6 (24.7 – 66.7)	0.02
Insulin average	11.6 (6.620.1)	9.7 (7.0-17.4)	0.17	42.2 (26.1 – 75.4)	21.6 (17.2 – 35.4)	0.02
TAUC Insulin	93.8 (60.5-121.0)	70.6 (47.1-124.3)	0.25	87.4 (55.2 – 172.3)	49.1 (37.8 – 81.2)	0.04
IAUC Insulin	74.6 (52.3 – 115.6)	64.1 (36.6 – 100.2)	0.24	82.9 (36.2 – 146.4)	34.9 (19.7 – 77.2)	0.03
Delta Insulin Final-Basal	40.0 (19.9-58.3)	28.4 (17.1-44.2)	0.06	33.7 (18.2 – 96.5)	21.8 (12.0-32.7)	0.09
Delta Insulin Max peak-Basal	57.7 (40.5-97.9)	46.8 (30.6-85.1)	0.19	56.6 (26.0 – 104.5)	29.3 (18.2 – 51.1)	0.01
Delta Insulin Max peak-Final	17.1 (0.0-42.5)	19.5 (0.0-43.3)	0.86	8.8 (0.0 – 35.0)	0.65 (0.0 – 12.8)	0.59

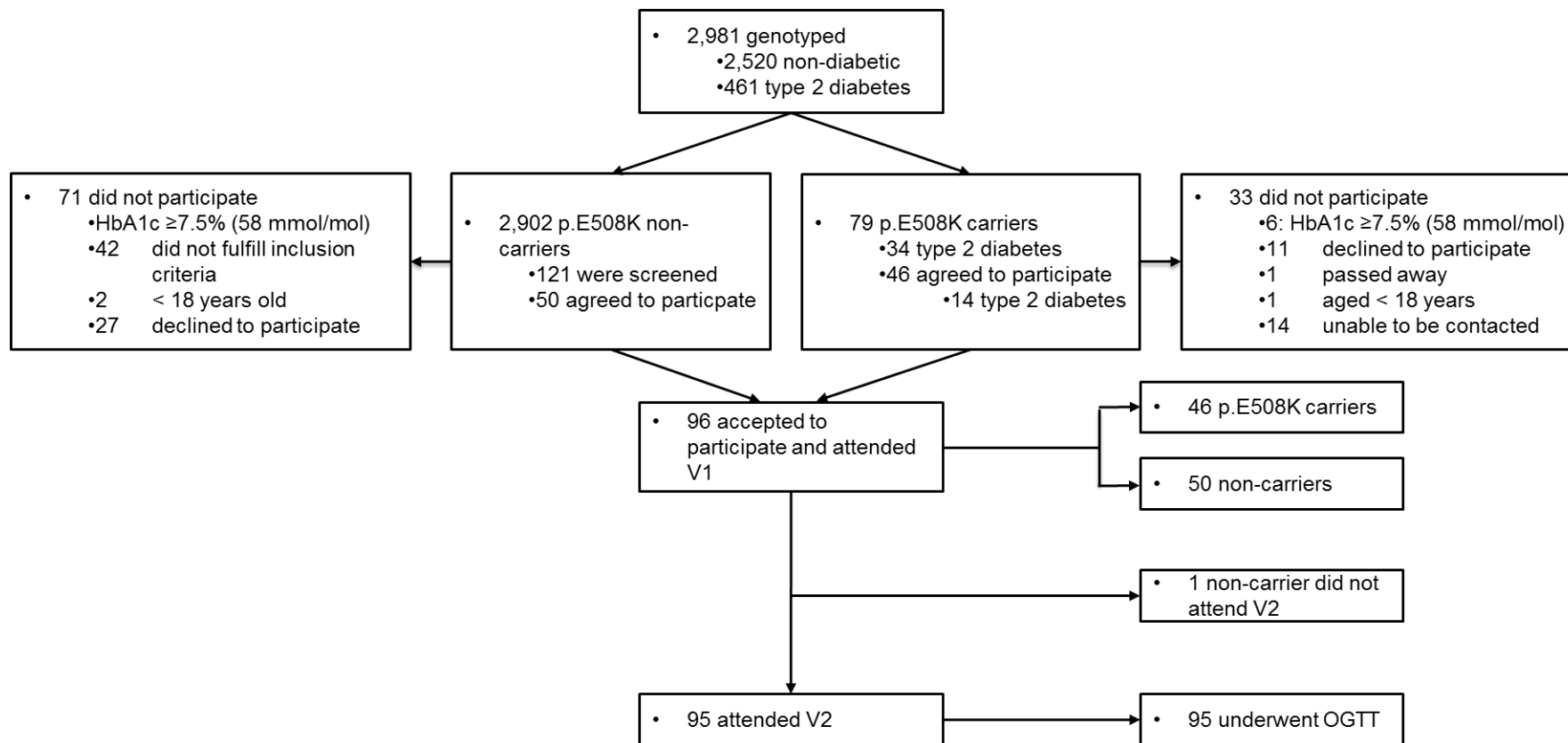
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Supplementary Table 3. Comparison of fasting and OGTT-based IR indexes comparing according to type 2 diabetes status between carriers and non-carriers. *Paired comparison between carriers (p=0.241) and non-carriers (p=0.488) without type 2 diabetes before and after metformin intake. †Paired comparison between carriers (p=0.149) and non-carriers with type 2 diabetes before and after metformin intake (p=0.628). *p-value* for comparison between carriers and non-carriers. Data are presented as Median and interquartile range (IQR).

Index	Without type 2 diabetes		p-value	Type 2 diabetes		p-value
	p.E508 (N=28)	p.E508K (N=32)		p.E508 (N=15)	p.E508K (N=15)	
HOMA-IR V1	2.45 (2.00-2.91)	1.96 (1.52-2.40)	0.13	3.46 (2.24-4.69)	2.97 (1.65-4.29)	0.23
HOMA-IR V2	2.64 (2.05-3.24)	1.80 (1.23-2.37)	0.046*	3.09 (2.17-4.02)	2.49 (1.53-3.44)	0.19†
Delta HOMA-IR	0.15 (-0.55-0.25)	-0.17 (-0.21-0.55)	0.25	-0.32 (-0.61-1.24)	-0.48 (-0.48-1.42)	0.81

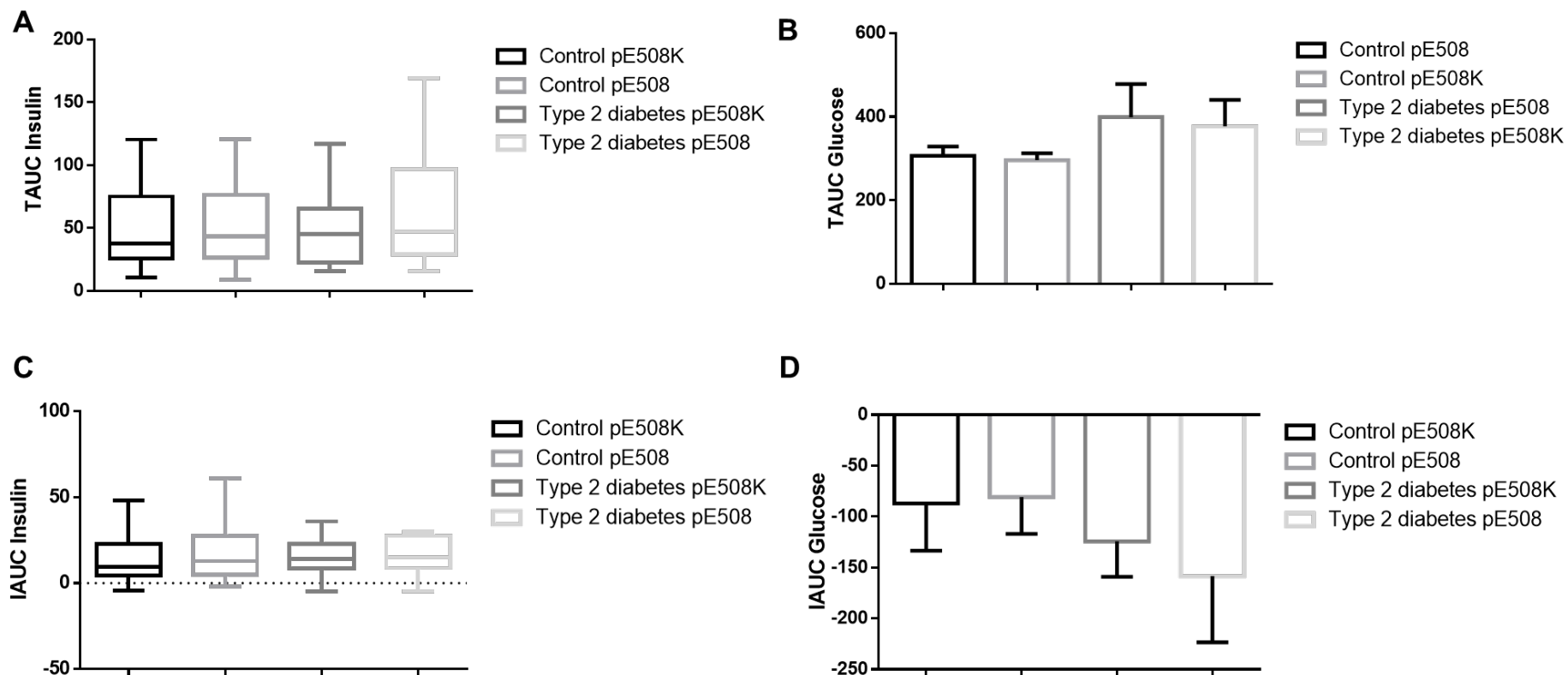
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Supplementary Figure 1. Recruitment flowchart of the study



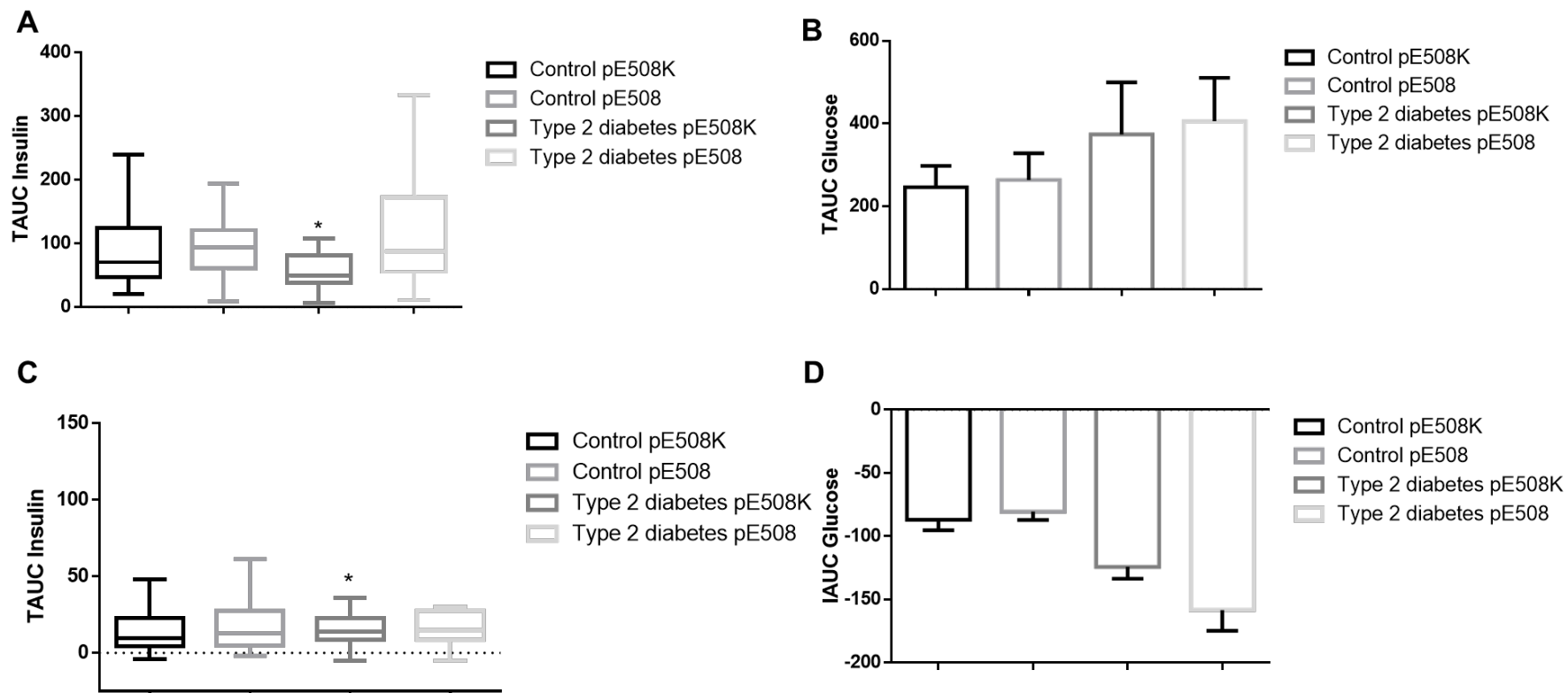
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Supplementary Figure 2. Comparison of insulin (A, C) and glucose (B, D) total areas under the curve (AUCT) and incremental areas under the curve (AUCI) after glipizide administration in carriers and non-carriers of the *HNF1A* pE508K variant with or without type 2 diabetes. Error bars \pm SD.



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Supplementary Figure 3. Comparison of insulin (A, C) and glucose (B, D) total areas under the curve (AUCT) and incremental areas under the curve (AUCI) after an oral glucose challenge (75g) and metformin 500 mg in carriers and non-carriers of the *HNF1A* pE508K variant with or without type 2 diabetes.



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