

SUPPLEMENTARY DATA

Supplementary Table 1. Associations between fasting glucose, fasting insulin and onset of depressive symptoms over 5-year follow-up in men (N = 2406)

		Odds of new-onset depressive symptoms							
		Model 1		Model 2		Model 3		Model 3_ND	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
	Q1	1	(ref)	1	(ref)	1	(ref)	1	(ref)
Glucose	Q2	0.73	0.40;1.33	0.73	0.40;1.32	0.73	0.40;1.33	0.69	0.37;1.27
Quintile	Q3	0.87	0.54;1.42	0.87	0.54;1.42	0.85	0.52;1.39	0.83	0.50;1.37
	Q4	0.65	0.37;1.14	0.65	0.37;1.14	0.64	0.36;1.13	0.64	0.36;1.12
	Q5	0.74	0.44;1.24	0.71	0.42;1.21	0.70	0.40;1.21	0.58	0.32;1.05
<i>P-value*</i>			0.57		0.54		0.53		0.34
	Q1	1	(ref)	1	(ref)	1	(ref)	1	(ref)
Insulin	Q2	1.05	0.62;1.78	1.05	0.62;1.78	1.03	0.60;1.77	0.97	0.56;1.68
Quintile	Q3	0.74	0.42;1.31	0.74	0.42;1.30	0.73	0.41;1.30	0.72	0.40;1.28
	Q4	0.92	0.54;1.59	0.92	0.53;1.58	0.96	0.54;1.70	0.90	0.50;1.63
	Q5	0.86	0.50;1.48	0.84	0.49;1.45	0.90	0.48;1.67	0.64	0.32;1.26
<i>P-value*</i>			0.77		0.76		0.40		0.58

Q refers to quintile.

Median and range (mmol/l) for fasting glucose quintiles were for Q1: 4.80 (3.10-4.90), Q2: 5.1 (5.00-5.10), Q3: 5.3 (5.20-5.40), Q4: 5.6 (5.50-5.70) and Q5: 6.1 (5.80-14.9)

Median and range (µU/ml) for fasting insulin quintiles were for Q1: 3.9 (3.10- 4.60), Q2: 5.4 (4.70- 6.20), Q3: 7.3 (6.30- 8.40), Q4: 9.8 (8.50- 11.9) and Q5: 16.4 (12.00-62.6)

Model 1: Model adjusted for age and ethnicity

Model 2: Model 1 additionally adjusted for type 2 diabetes prevalence at baseline.

Model 3: Model 2 additionally adjusted for occupational grade, marital status, smoking, stroke, coronary heart disease, hypertension, HDL-cholesterol, use of lipid-lowering drugs, central obesity, and cognitive impairment

Model 3_ND: Model 3 restricted to non-diabetic participants (n=2242).

*P-value for tests of overall heterogeneity in odds ratios of new-onset depressive symptoms.

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Supplementary Table 2. Associations between fasting glucose, fasting insulin, and onset of depressive symptoms over 5-year follow-up in women (N = 739)

		Odds of new-onset depressive symptoms by							
		Model 1		Model 2		Model 3		Model 3_ND	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
	Q1	1	(ref)	1	(ref)	1	(ref)	1	(ref)
Glucose	Q2	1.70	0.89;3.26	1.70	0.89;3.27	1.66	0.86;3.24	1.74	0.90;3.39
Quintile	Q3	1.44	0.77;2.70	1.44	0.77;2.71	1.37	0.72;2.61	1.30	0.67;2.51
	Q4	1.80	0.87;3.73	1.80	0.87;3.75	2.01	0.95;4.25	1.91	0.89;4.10
	Q5	1.01	0.43;2.37	1.04	0.43;2.53	1.20	0.49;2.96	1.20	0.46;3.15
<i>P-value*</i>			0.36		0.37		0.37		0.39
	Q1	1	(ref)	1	(ref)	1	(ref)	1	(ref)
Insulin	Q2	0.56	0.29;1.06	0.56	0.29;1.07	0.49	0.25;0.97	0.49	0.24;0.98
Quintile	Q3	0.48	0.24;0.98	0.48	0.24;0.98	0.44	0.21;0.94	0.48	0.22;1.03
	Q4	0.61	0.31;1.18	0.61	0.31;1.18	0.57	0.27;1.19	0.62	0.29;1.32
	Q5	0.38	0.17;0.85	0.38	0.17;0.86	0.38	0.15;0.96	0.51	0.20;1.30
<i>P-value*</i>			0.09		0.10		0.12		0.23

Q refers to quintile.

Median and range (mmol/l) for fasting glucose quintiles were for Q1: 4.80 (3.10-4.90), Q2: 5.1 (5.00-5.10), Q3: 5.3 (5.20-5.40), Q4: 5.6 (5.50-5.70) and Q5: 6.1 (5.80-14.9)

Median and range (µIU/ml) for fasting insulin quintiles were for Q1: 3.9 (3.10- 4.60), Q2: 5.4 (4.70- 6.20), Q3: 7.3 (6.30- 8.40), Q4: 9.8 (8.50- 11.9) and Q5: 16.4 (12.00-62.6)

Model 1: Model adjusted for age and ethnicity

Model 2: Model 1 additionally adjusted for type 2 diabetes prevalence at baseline.

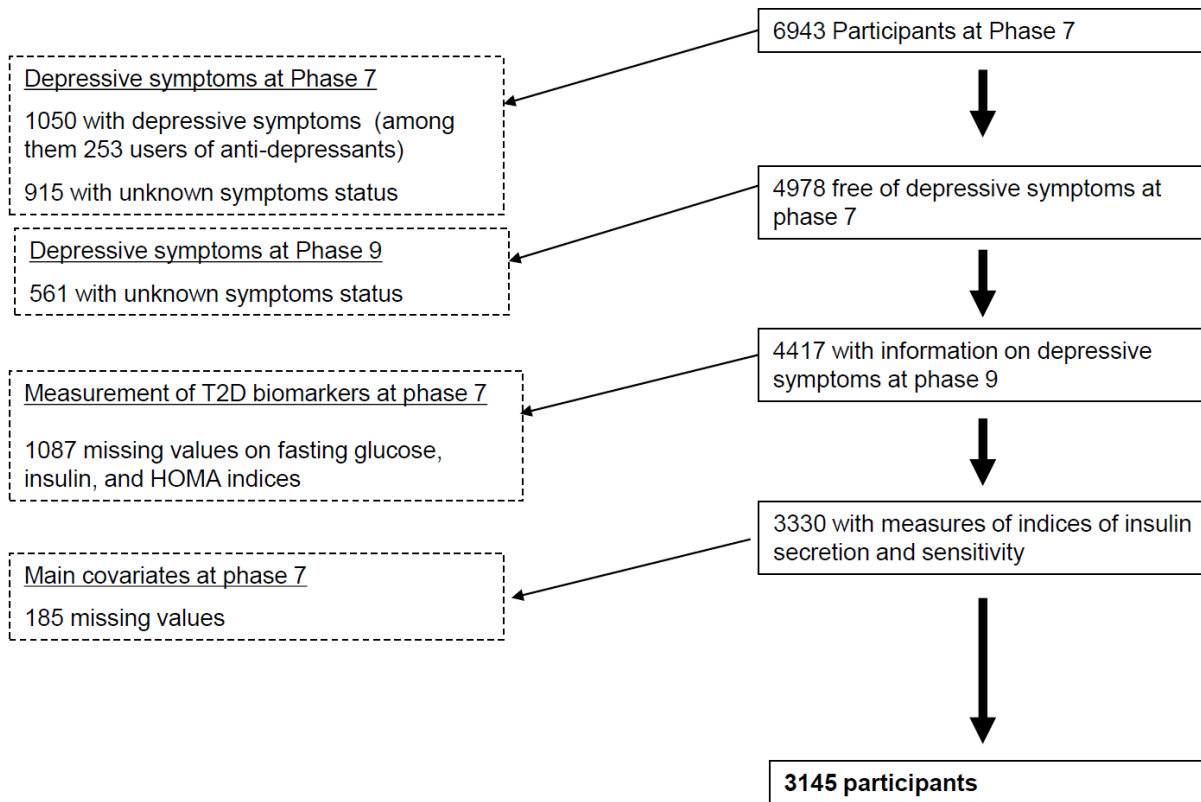
Model 3: Model 2 additionally adjusted for occupational grade, marital status, smoking, stroke, coronary heart disease, hypertension, HDL-cholesterol, use of lipid-lowering drugs, central obesity, and cognitive impairment

Model 3_ND: Model 3 restricted to non-diabetic participants (n=687).

*P-value for test of overall heterogeneity in odds ratios of new-onset depressive symptoms.

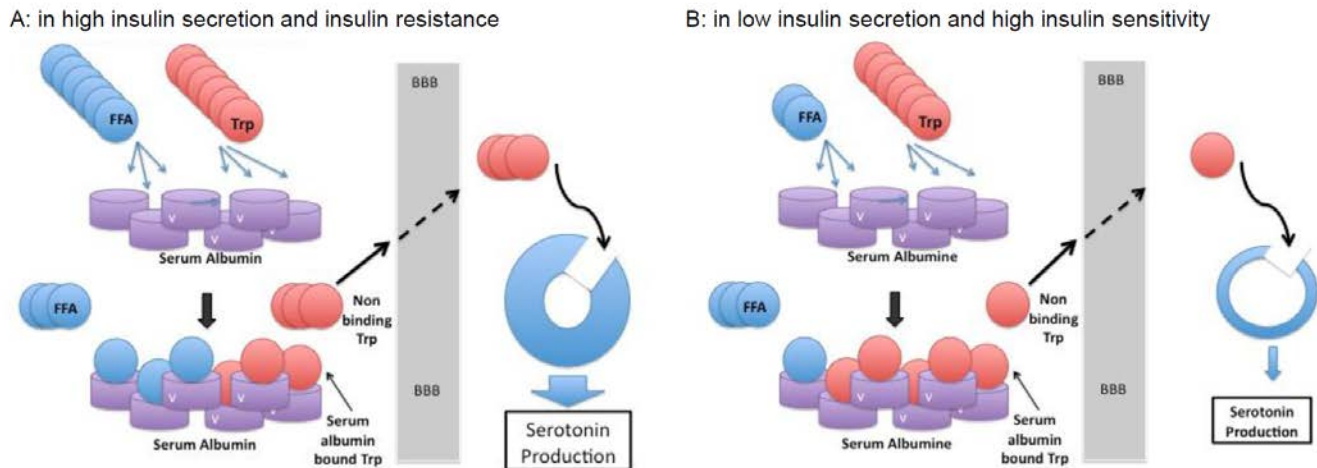
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Supplementary Figure 1. Flow chart mapping the selection of the 3145 Whitehall II participants included in the present analyses



SUPPLEMENTARY DATA

Supplementary Figure 2. Illustration of a hypothesized mechanism (initially proposed by Golomb et al.) linking insulin secretion with central serotonin synthesis



Part A: In a state of high insulin secretion induced by an insulin resistance, increased level of postprandial free fatty acids (FFA) is observed that competes with Tryptophan (Trp) for binding to serum albumin. The free (non serum albumin bound) Trp readily crosses the blood brain barrier (BBB) and enters the serotonin production cycle where free Trp constitutes a rate limiting substrate.

Part B: In a state of low insulin secretion with high insulin sensitivity, FFA release is suppressed, leading to a reduced pool of FFA. With Low FFA levels more albumin is available to bind tryptophan, reducing the free tryptophan fraction, leading to reduced synthesis of serotonin in the central nervous system.