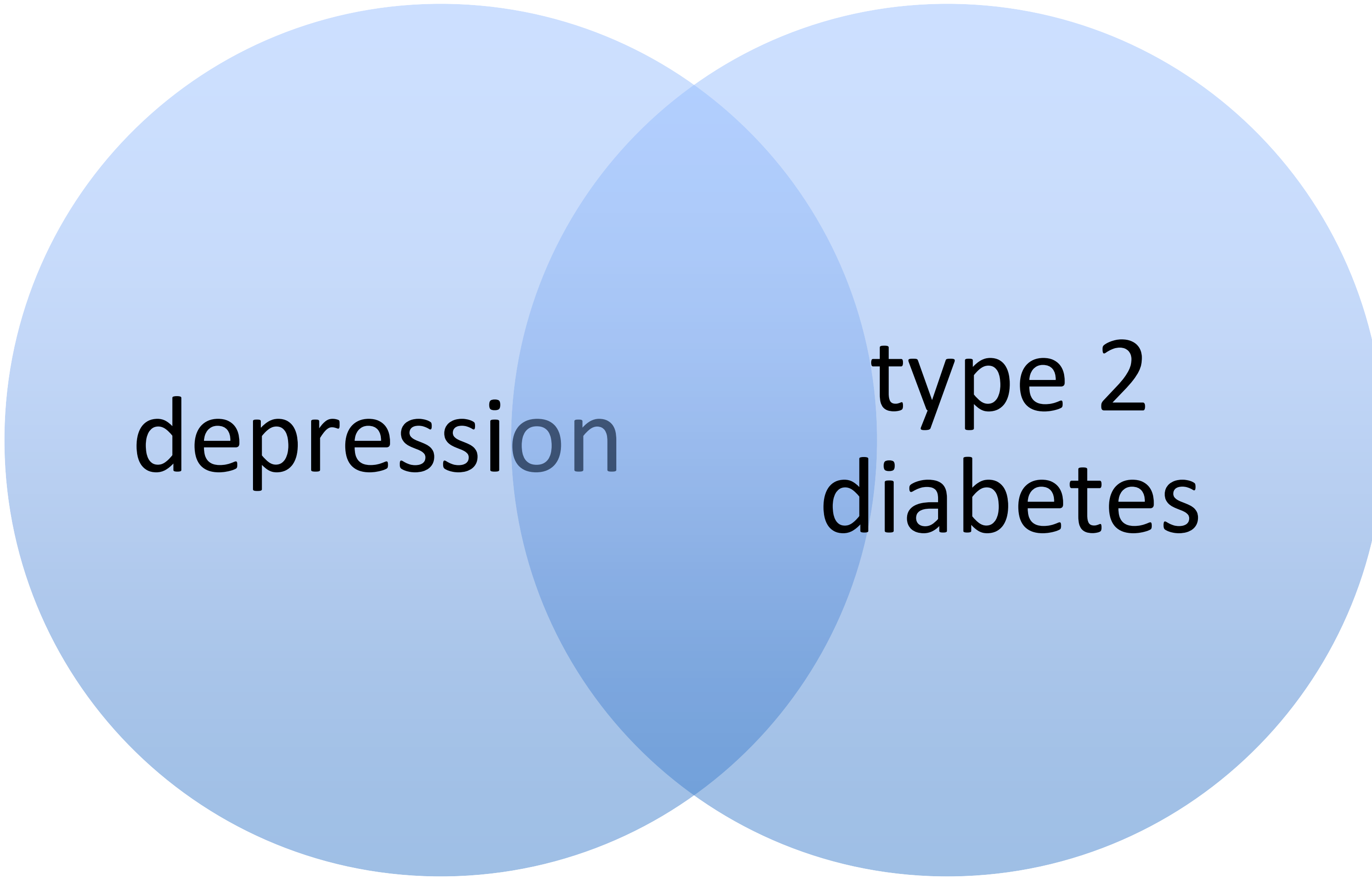
# Diabetes: the future includes psychiatry!

Khalida Ismail

78th UWI/BAMP CME

14th November 2015

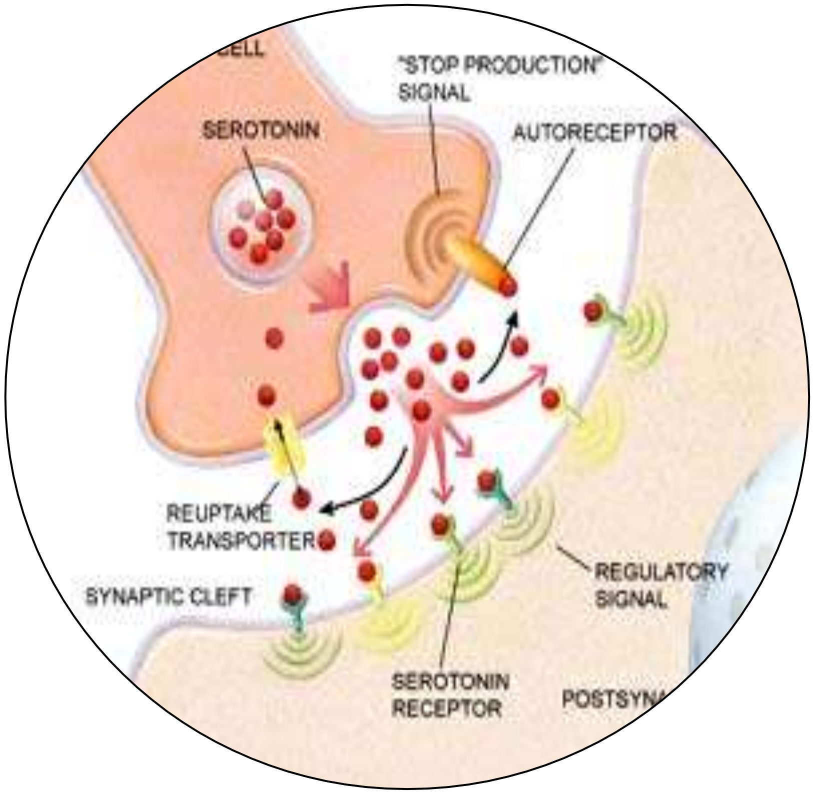
# Depression-diabetes link



# Overview

- Epidemiology of depression in type 2 diabetes
- Theoretical model for shared biological mechanisms
- Evidence for a shared inflammatory model

# Depression


"STOP PRODUCTION"
SIGNAL
SEROTONIN
AUTORECEPTOR
REUPTAKE
TRANSPORTER
SYNAPTIC CLEFT
REGULATORY
SIGNAL
SEROTONIN
RECEPTOR

*I'm right there in the room and no one even acknowledges me*

# Depression*

**At least 2 core symptoms**

Low mood

Anhedonia

Fatigue

**At least 2 additional symptoms**

Appetite/weight

Sleep

Concentration

Psychomotor function

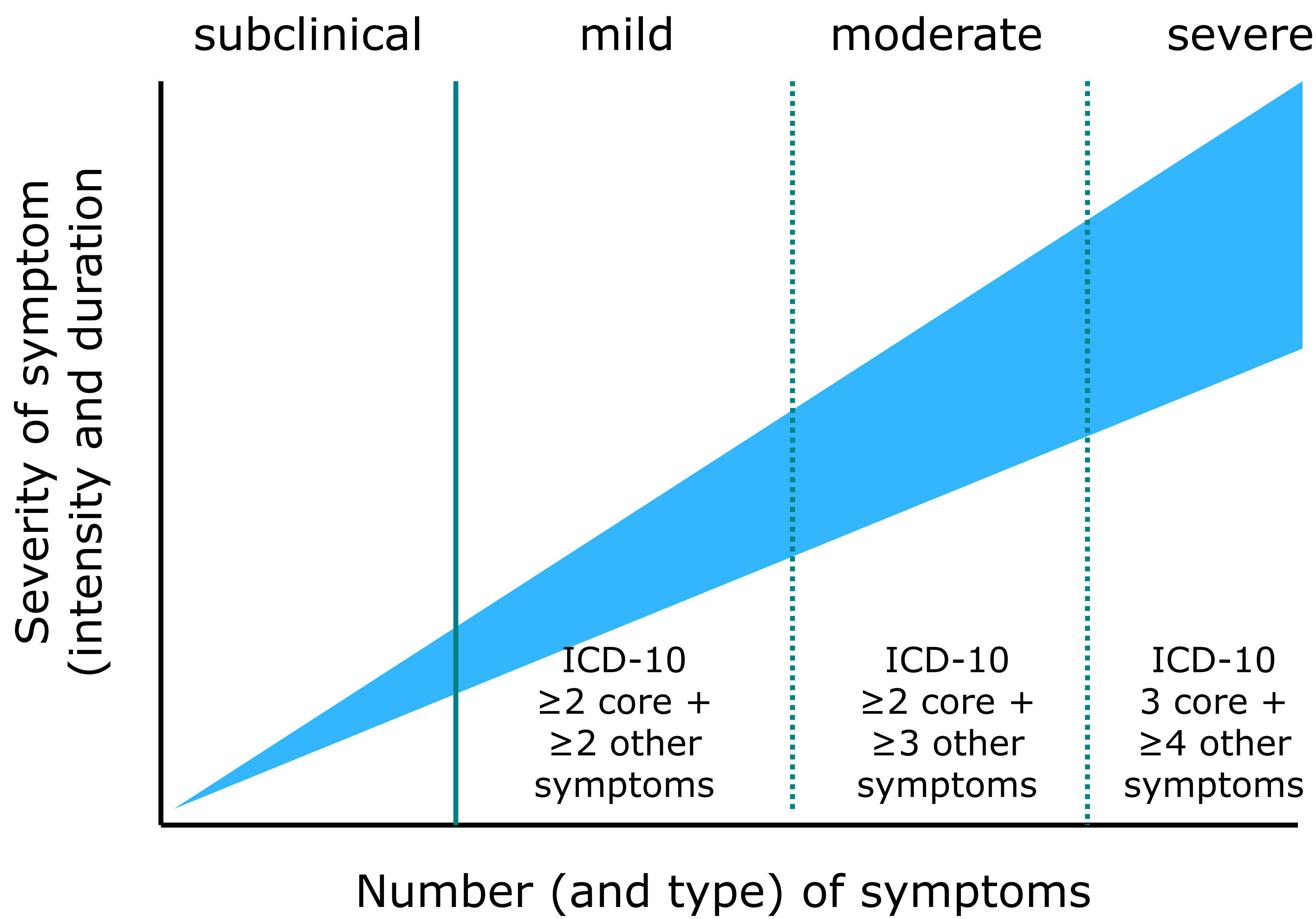
Suicidal ideation

Guilt

Self esteem

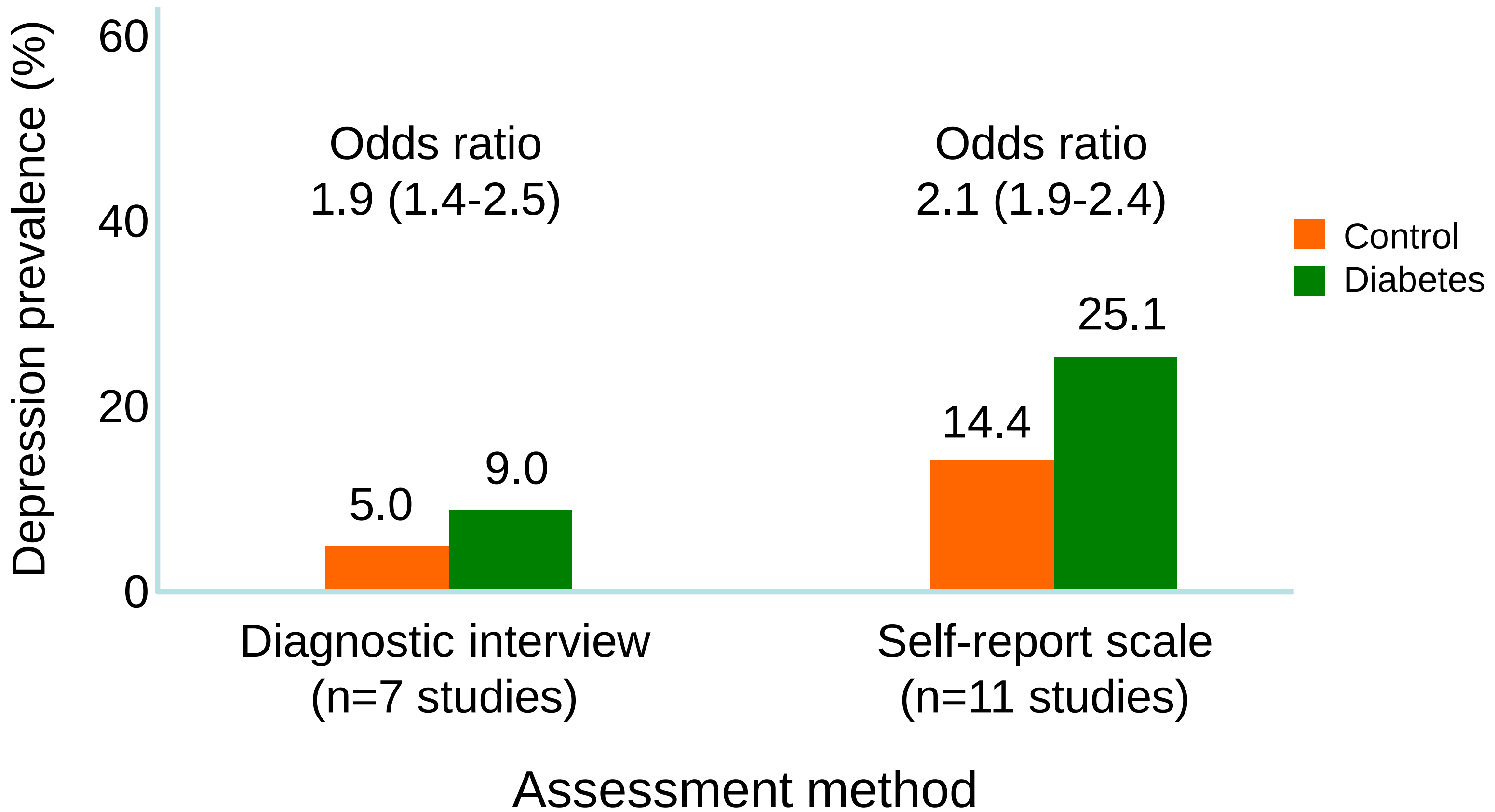
* change in these symptoms, and they should be present most of the day, most days of the week, at least 2 weeks
http://apps.who.int/classifications/icd10

# Depression is a continuous construct with arbitrary categories




www.who.int/classifications/icd

# The pooled prevalence of depression is increased two-fold in diabetes




Anderson et al Diabetes Care 2001

# Depression and mortality in people with their first diabetic foot ulcer (n=253)

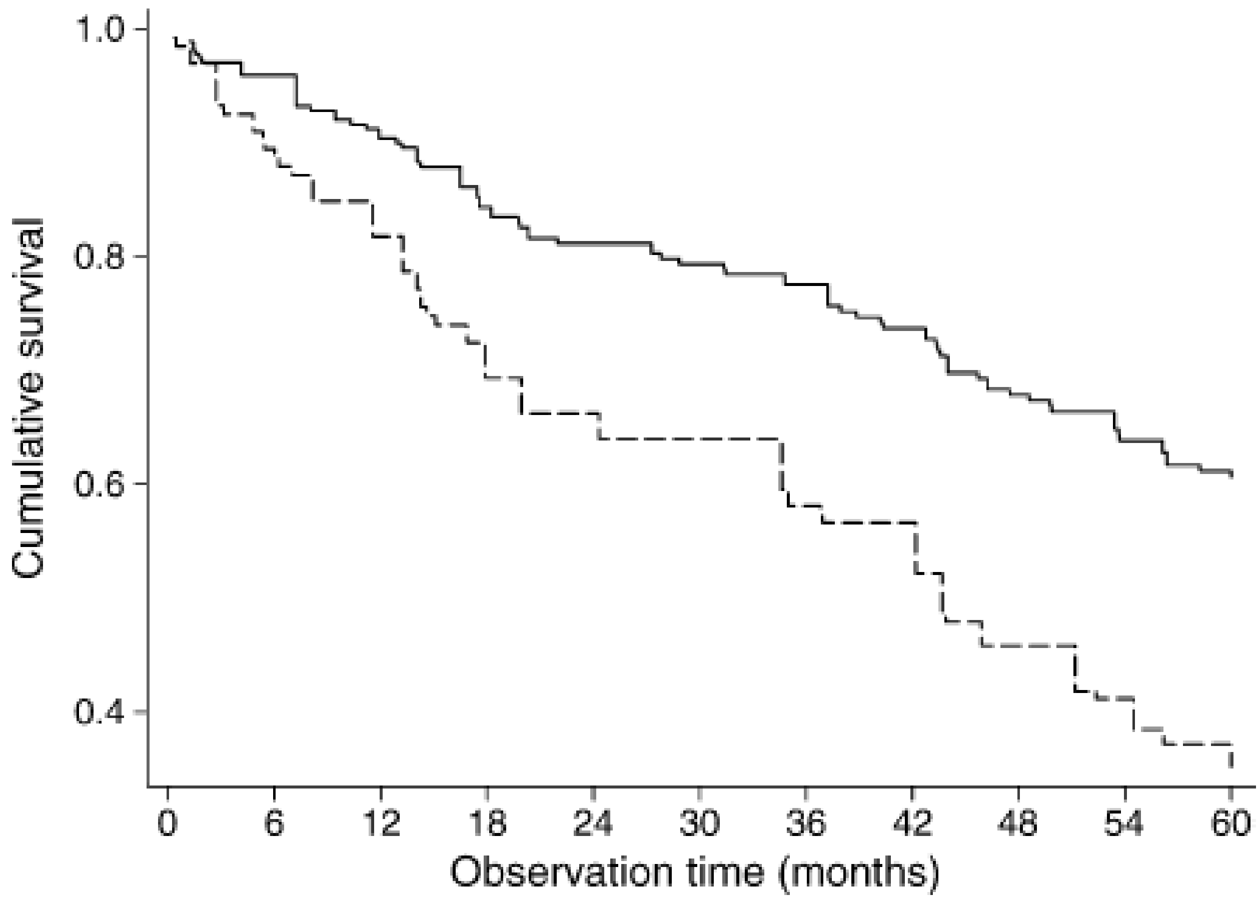



**Fig. 2** Predicted survival curve for participants with and without depression. Solid line, not depressed; dashed line, depressed

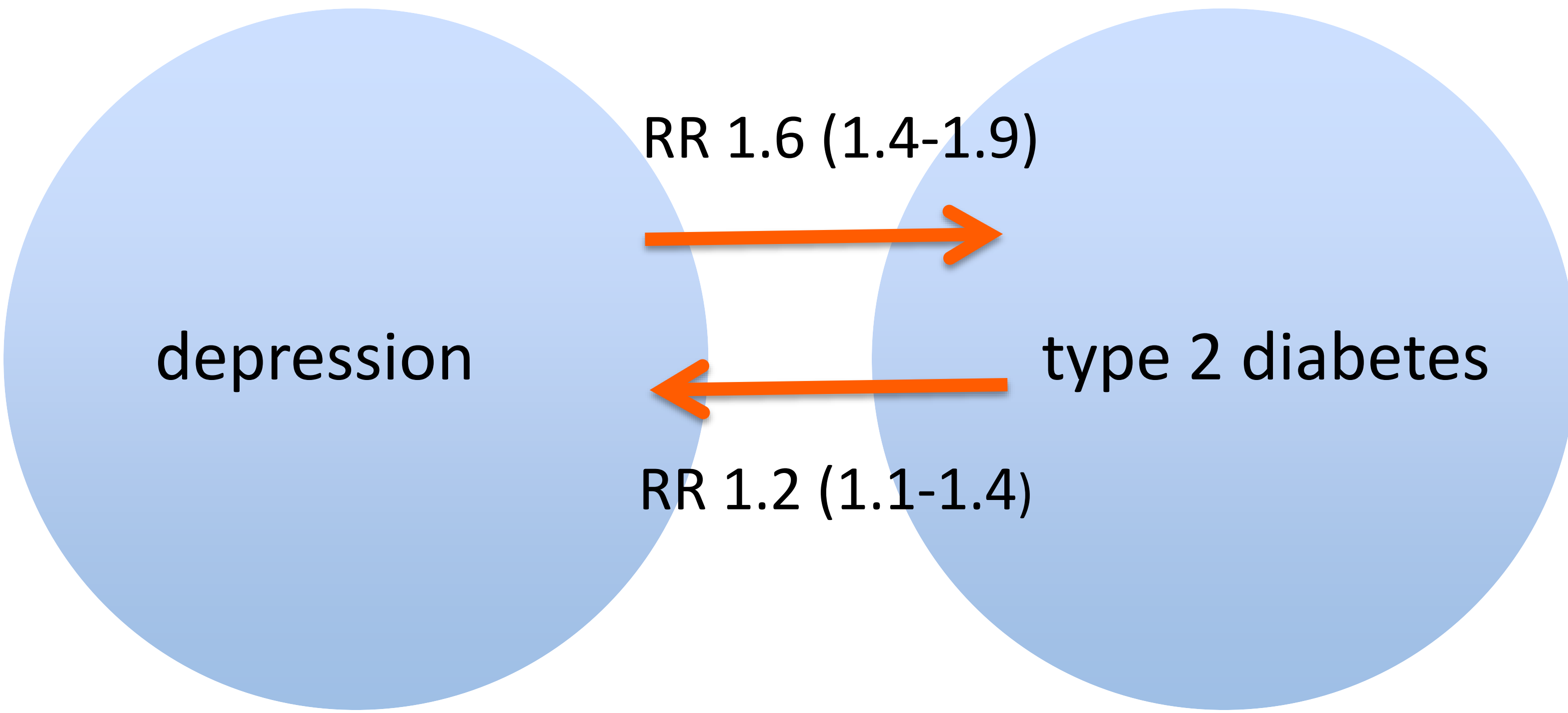

Ismail K, Winkley K, Stahl D, Chalder T, Edmonds M. Diabetes Care 2007:30;1473-9

Winkley K, Sallis H, Kariyawasam D, Leelarathra L, Chalder T, Edmonds M, Stahl D, Ismail K. Diabetologia 2012;155:303-10



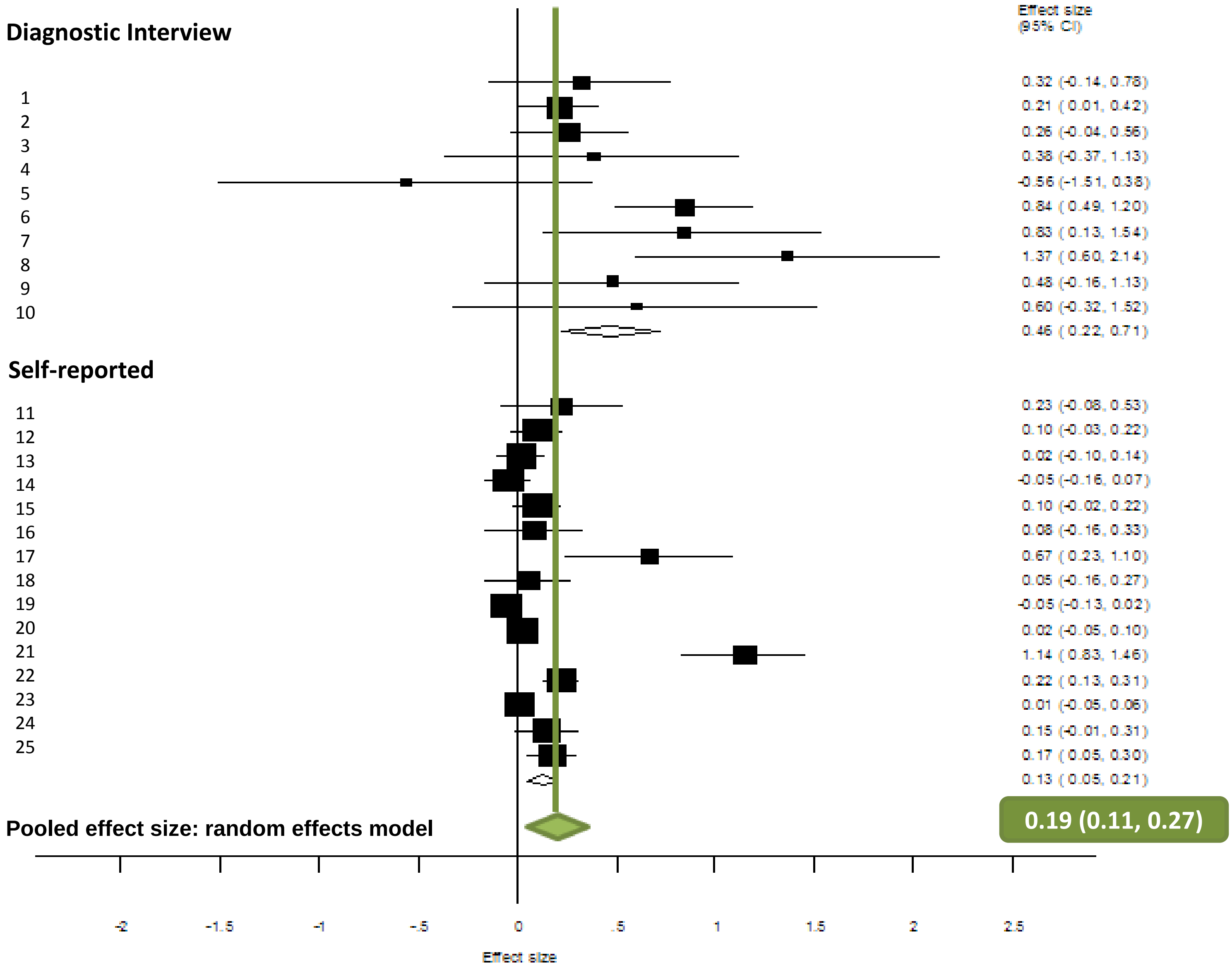
Funding: Wellcome Trust

# Bidirectional association between depression and type 2 diabetes



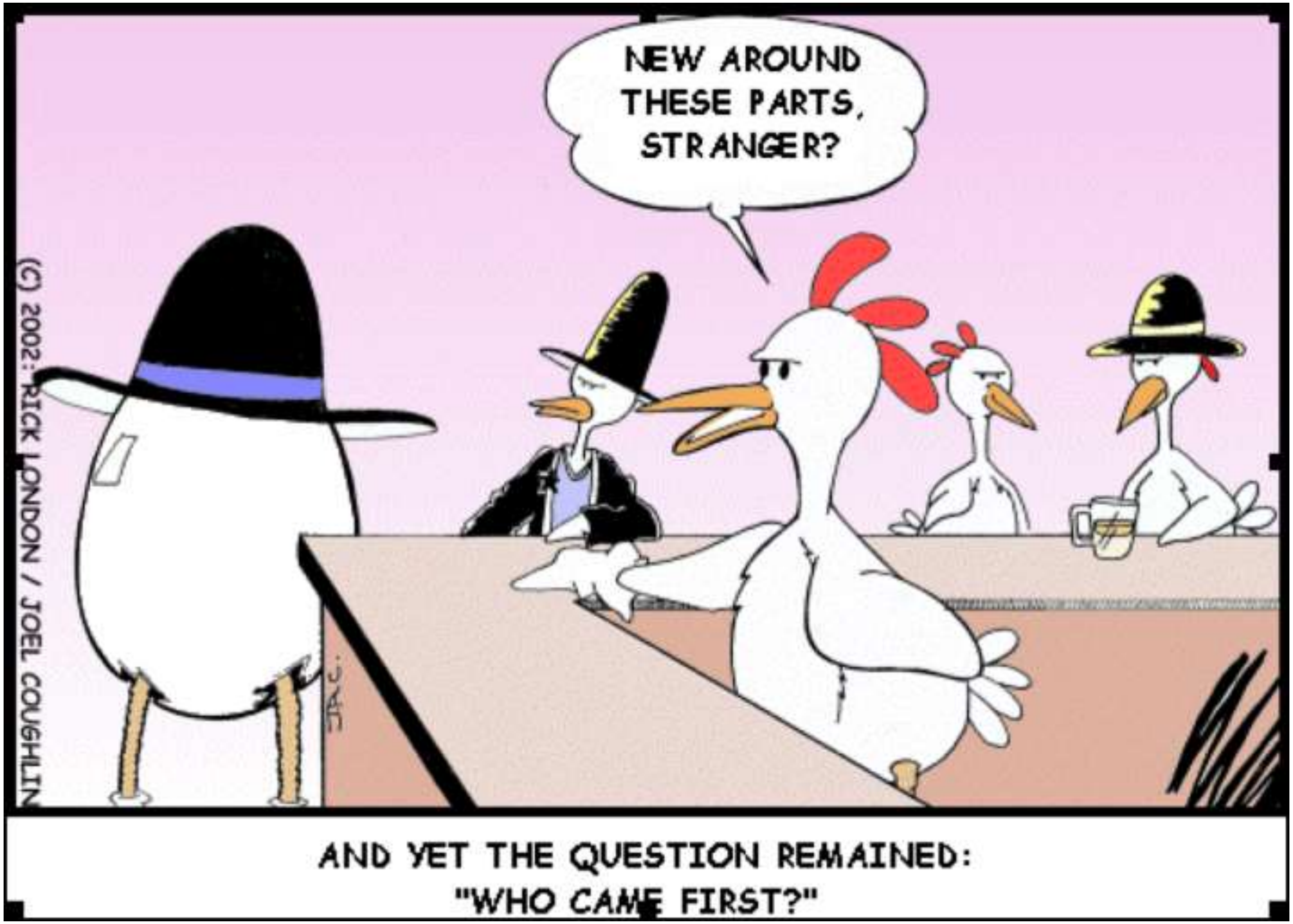

Mezuk et al Diabetes Care 2008;31:2383-90
Nouwen A, Winkley K, Twisk J, Lloyd CE, Peyrot M, Ismail K, Pouwer F. Diabetologia 2010;53:2480-6

# Meta-analysis of the association between depression and insulin resistance



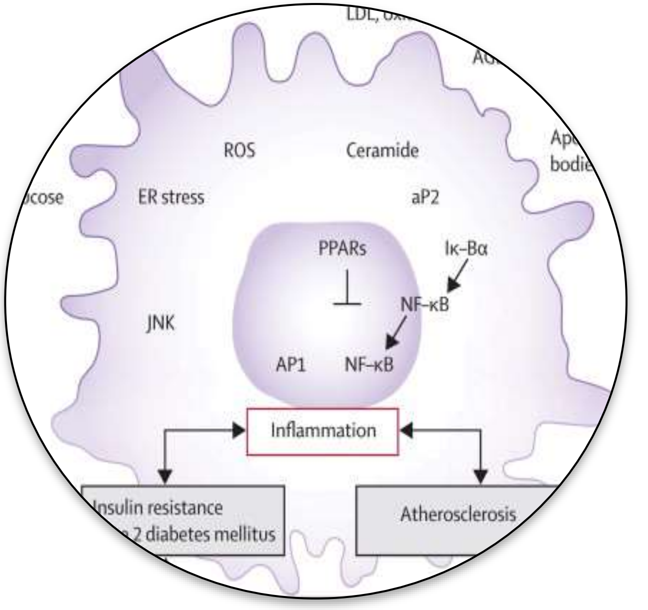

**Pooled effect size (95% confidence interval): 0.19 (0.11-0.27)**

Kan C, Silva N, Golden SH, Rajala U, Timonen M, Stahl D, Ismail K. Diabetes Care. 2013;36:480-9

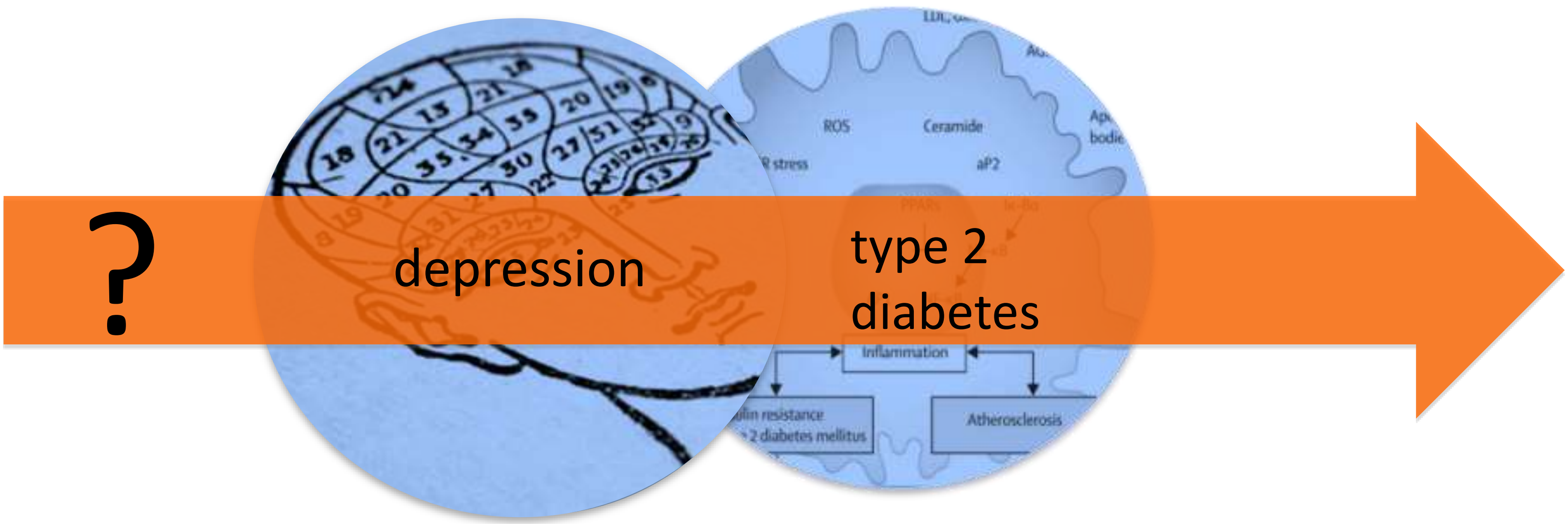

NEW AROUND THESE PARTS, STRANGER?
(C) 2002: RICK LONDON / JOEL COUGHLIN
AND YET THE QUESTION REMAINED: "WHO CAME FIRST?"

# Biological mechanisms

- HPA axis
- innate inflammation
- autonomic nervous system
- early life programming
- antidepressants
- circadian clock
- gut hormones and satiety
- sleep apnoea
- mitochondria



# Depression-diabetes link=? inflammation




Pickup JC, Mattock MB, Chusney GD, Burt D. Diabetologia 1997;40:1286–1292

# Multiple effects of the innate immune response

ENVIRONMENTAL THREATS/TOXINS: obesity, sedentary lifestyle, smoking, chronic social and psychological adversity

↓

MACROPHAGES: pro-inflammatory (IL-6, IL-1, TNF-$\alpha$) and anti-inflammatory cytokines (adiponectin)→ 'sickness behaviors'

↓

ACUTE-PHASE RESPONSE: blood proteins (C-reactive protein (CRP), serum amyloid A) and triglycerides

↓

CELL DAMAGE: Pancreatic $\beta$-cells, insulin resistance, endothelial (arterial), neuroglia (brain cells)

↓

DISEASE: type 2 diabetes, arthrosclerosis, depression, cognitive impairment

Funding NIHR and EFSDC

KING'S DIABETES AND MENTAL HEALTH

SOULD

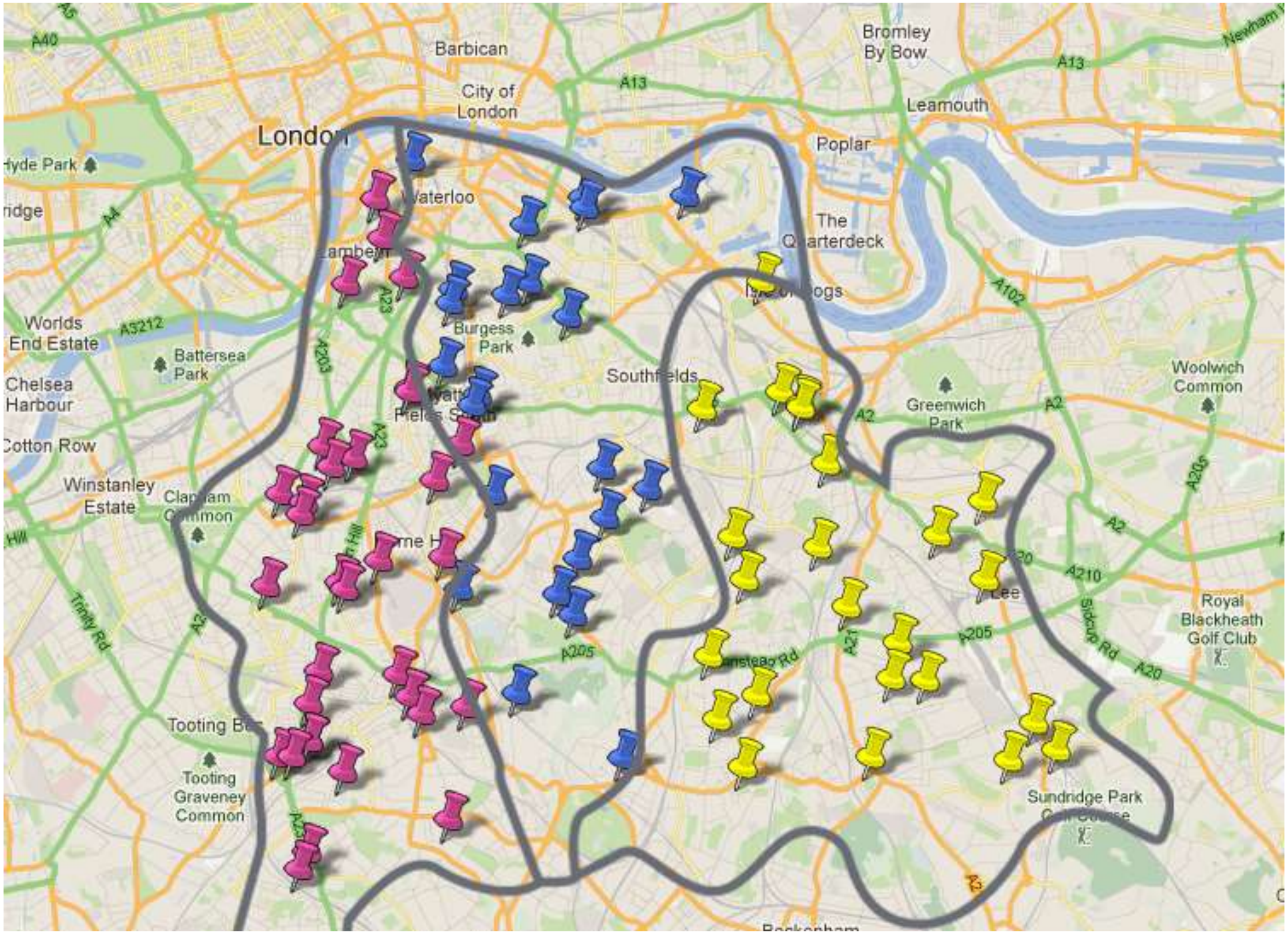
# SOUth London Diabetes Cohort Study

**Funding: NIHR Programme Grant**

# SOUL-D

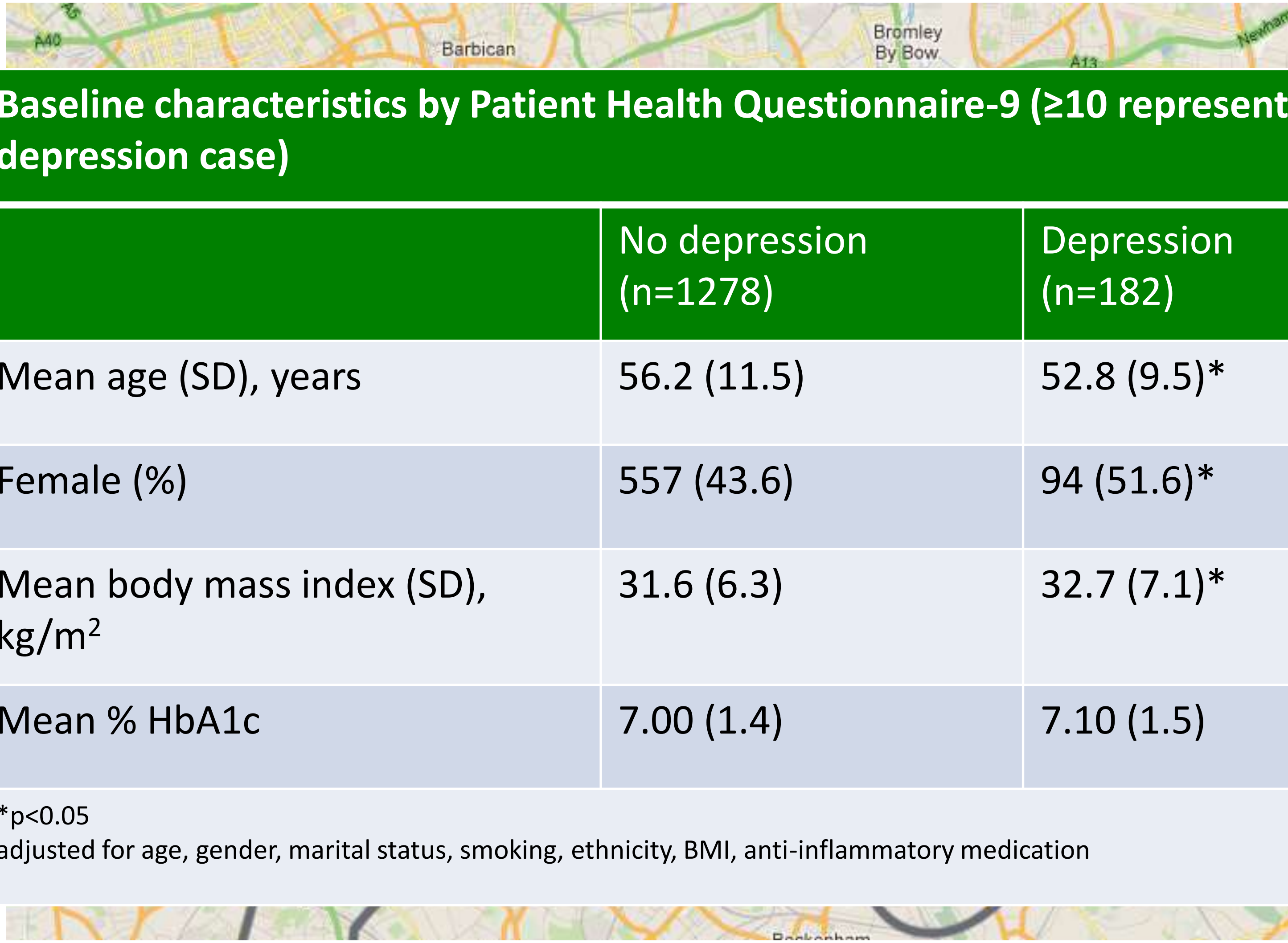
a prospective cohort study in primary care to test the effect of depression on biomedical, psychological and social outcomes in new onset type 2 diabetes over 2 years

# Setting of SOUL-D




Lambeth Southwark Lewisham n= 96/139 surgeries

# Setting of SOUL-D



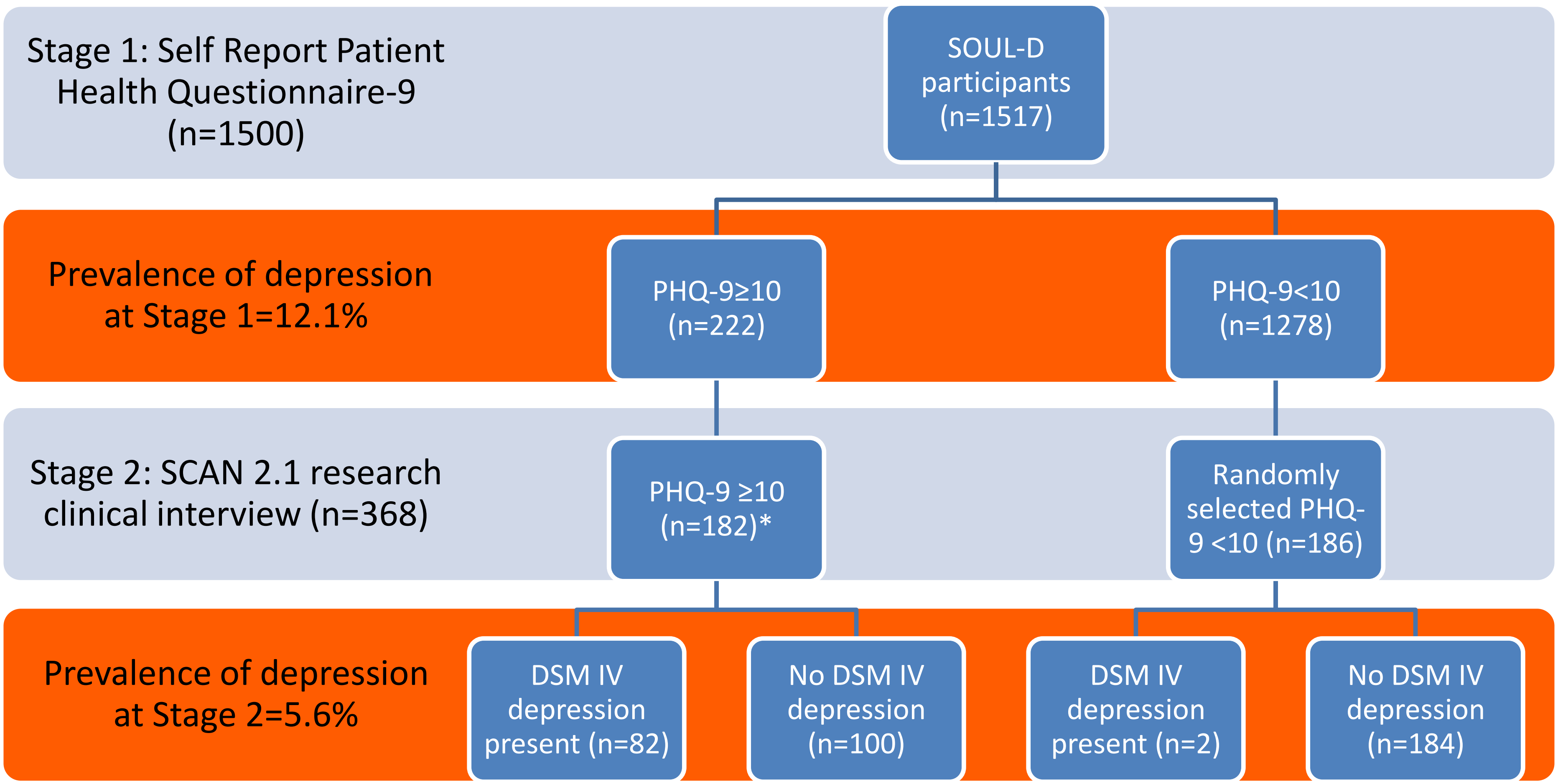

**Baseline characteristics by Patient Health Questionnaire-9 (≥10 represents depression case)**

| | No depression (n=1278) | Depression (n=182) |
|---|---|---|
| Mean age (SD), years | 56.2 (11.5) | 52.8 (9.5)* |
| Female (%) | 557 (43.6) | 94 (51.6)* |
| Mean body mass index (SD), $kg/m^2$ | 31.6 (6.3) | 32.7 (7.1)* |
| Mean % HbA1c | 7.00 (1.4) | 7.10 (1.5) |

*$p<0.05$
adjusted for age, gender, marital status, smoking, ethnicity, BMI, anti-inflammatory medication

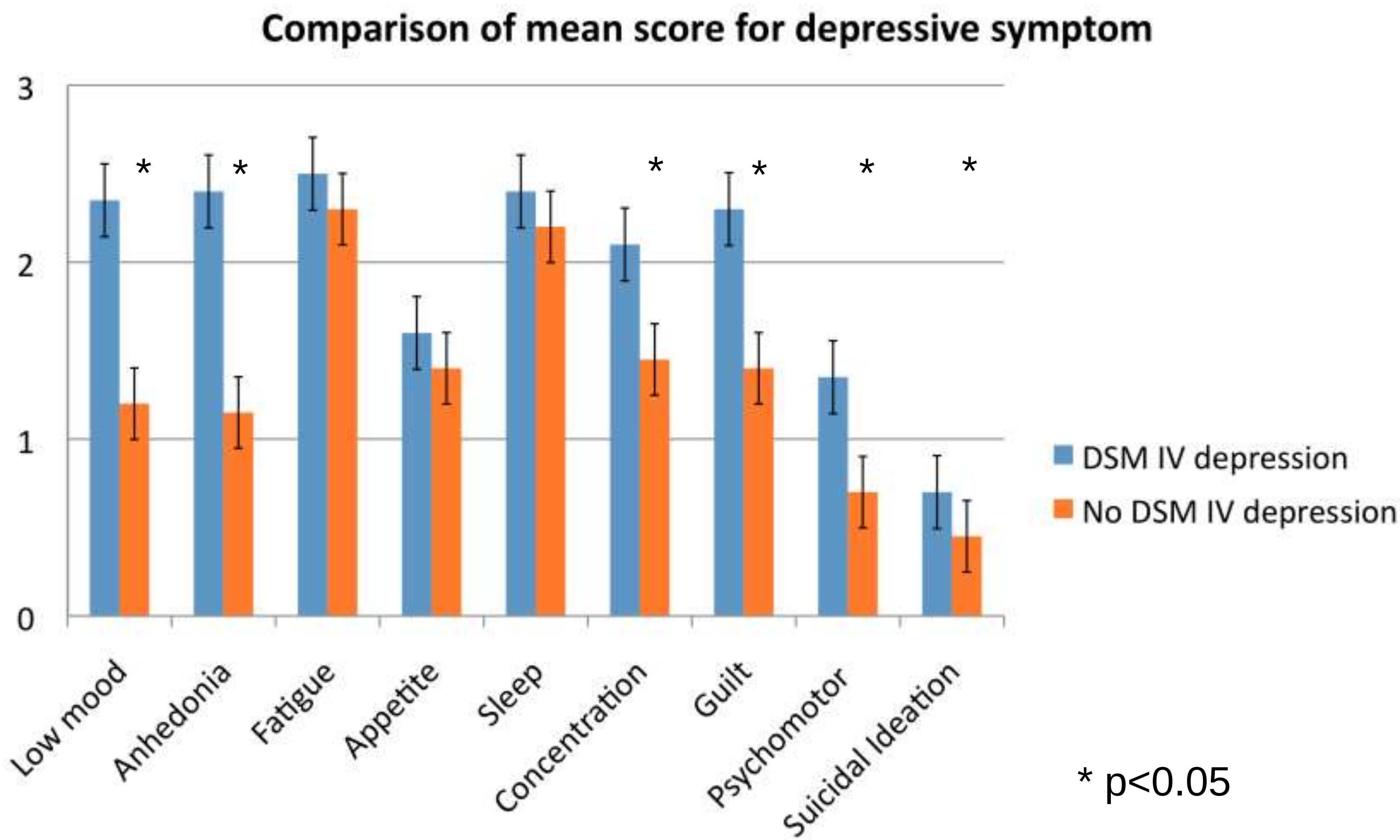
**Lambeth Southwark Lewisham** n= 96/139 surgeries

# Prevalence of depression in SOUL-D



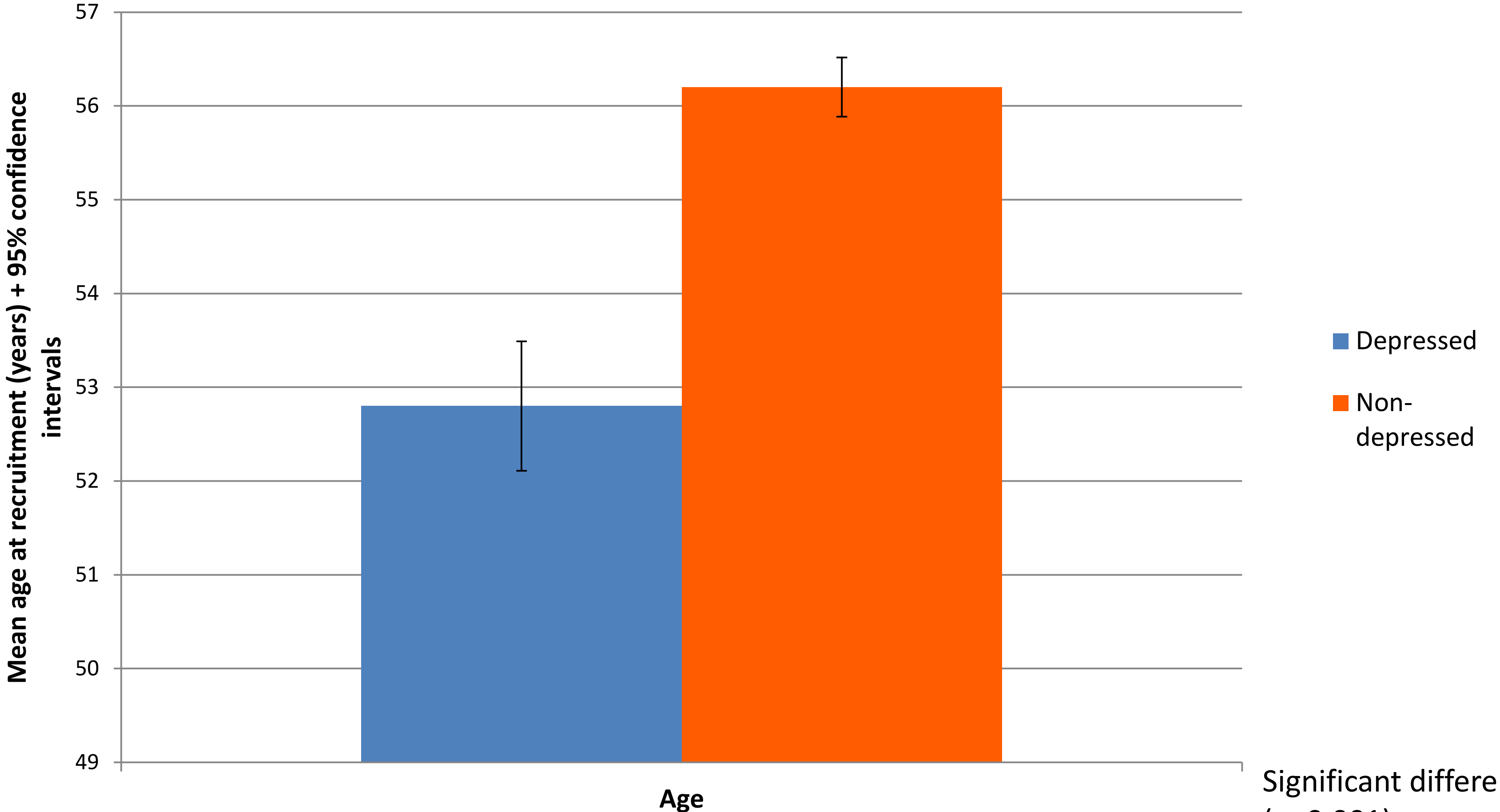

Twist, K, Stahl D, Amiel S, Thomas S, Winkley K, Ismail K
Psychosomatic Medicine 2013 75:791-7

* Missing data on n=40 patients




Twist, K, Stahl D, Amiel S, Thomas S,  Winkley K, Ismail K
Psychosomatic Medicine 2013;75:791-7

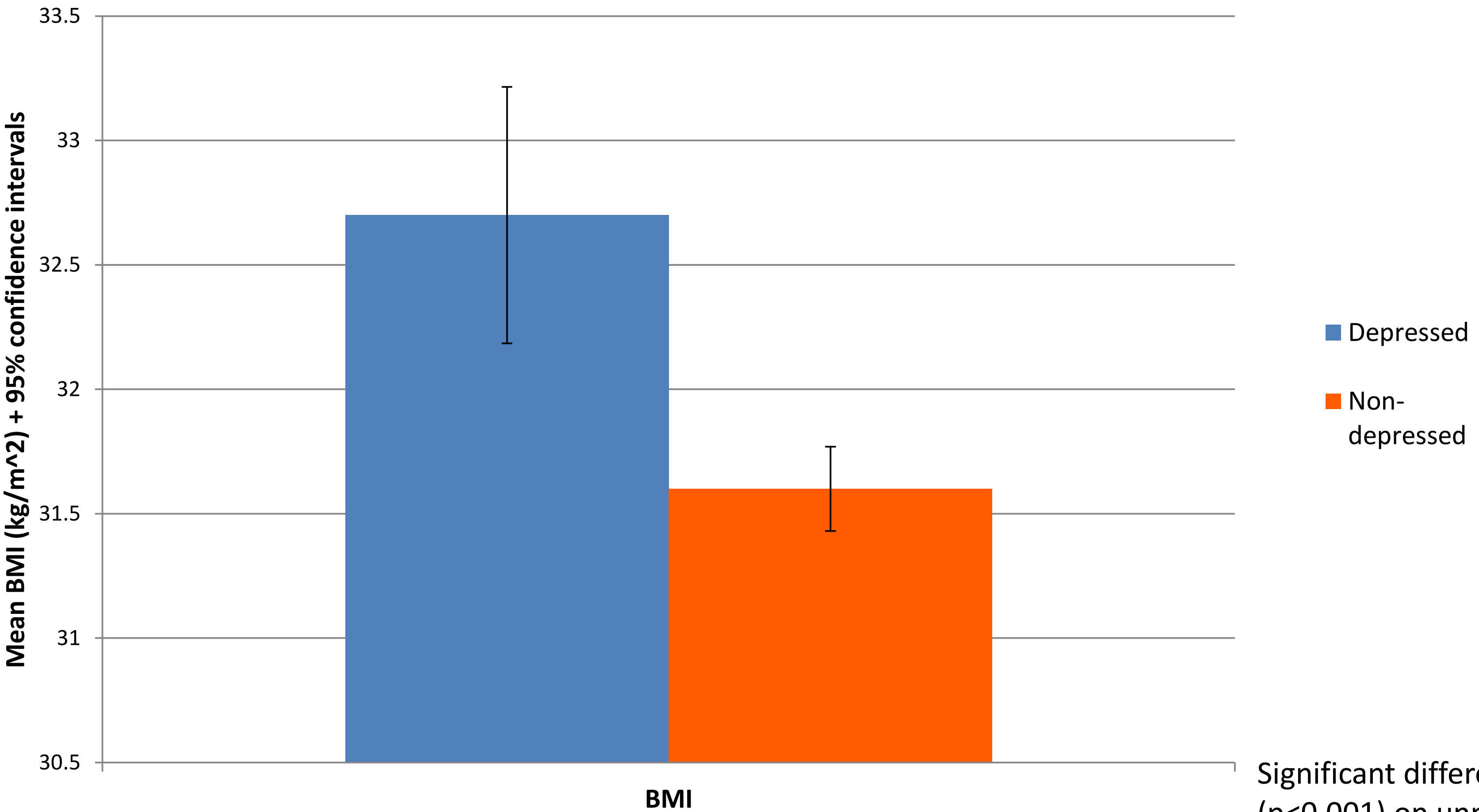
# Patients with depression are younger




Significant difference ($p<0.001$)

Twist, K, Stahl D, Amiel S, Thomas S, Winkley K, Ismail K
Psychosomatic Medicine 2013 75:791-7

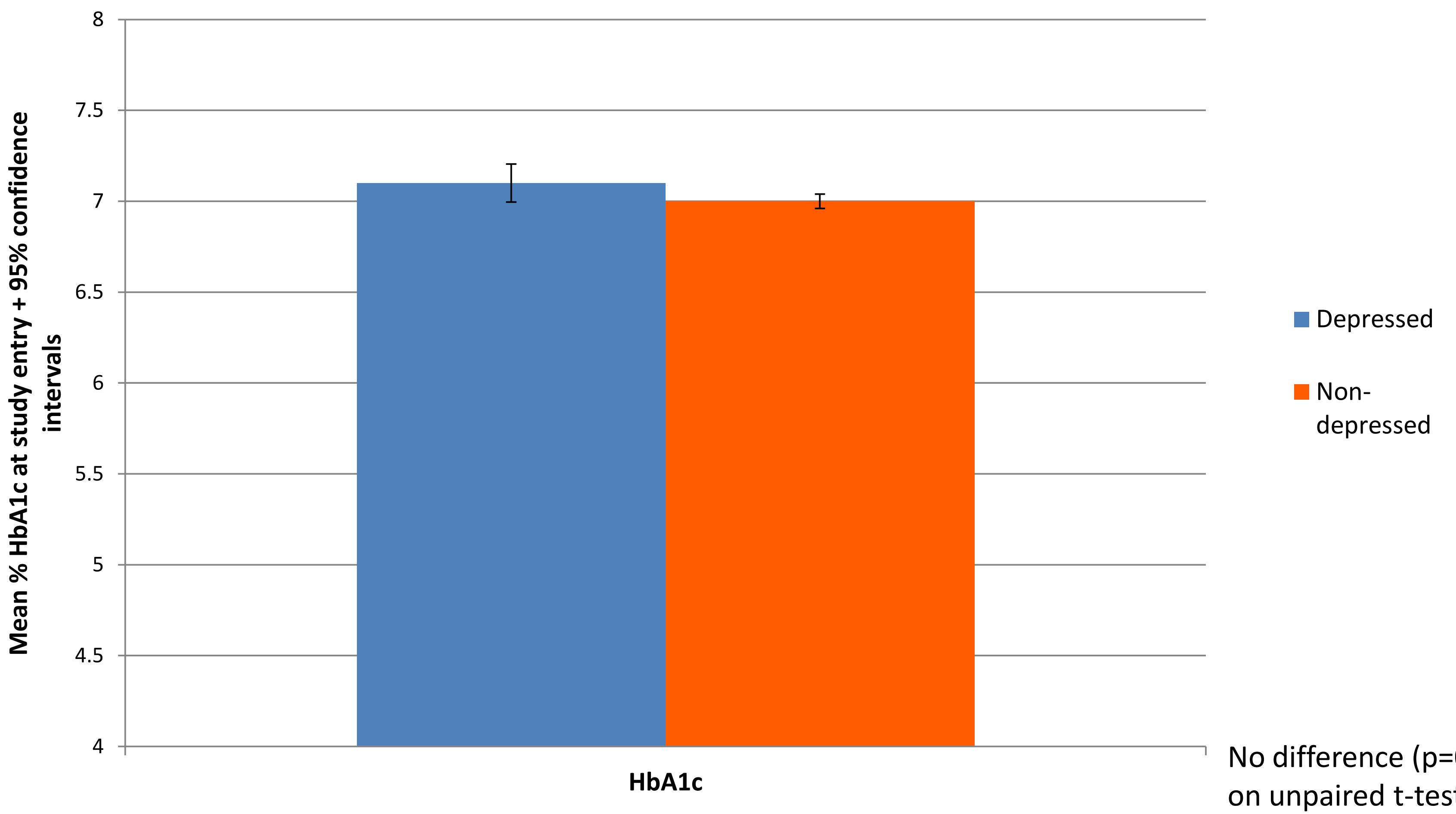
# Patients with depression have higher body mass index




Significant difference ($p<0.001$) on unpaired t-test

Twist, K, Stahl D, Amiel S, Thomas S, Winkley K, Ismail K
Psychosomatic Medicine 2013 75:791-7

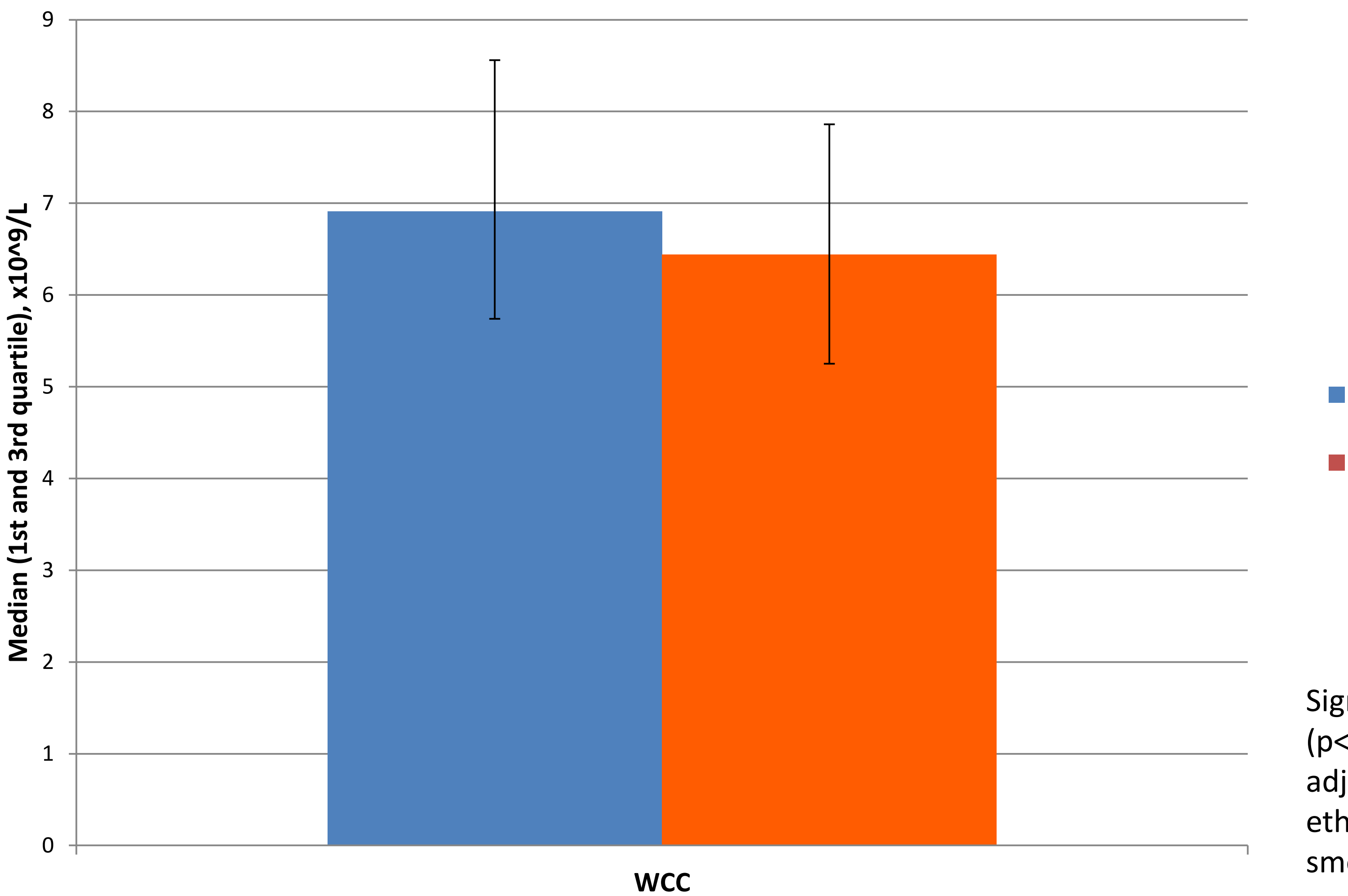
# Patients with depression had the same HbA1c as those not depressed




No difference (p=0.38) on unpaired t-test

Twist, K, Stahl D, Amiel S, Thomas S, Winkley K, Ismail K
Psychosomatic Medicine 2013 75:791-7

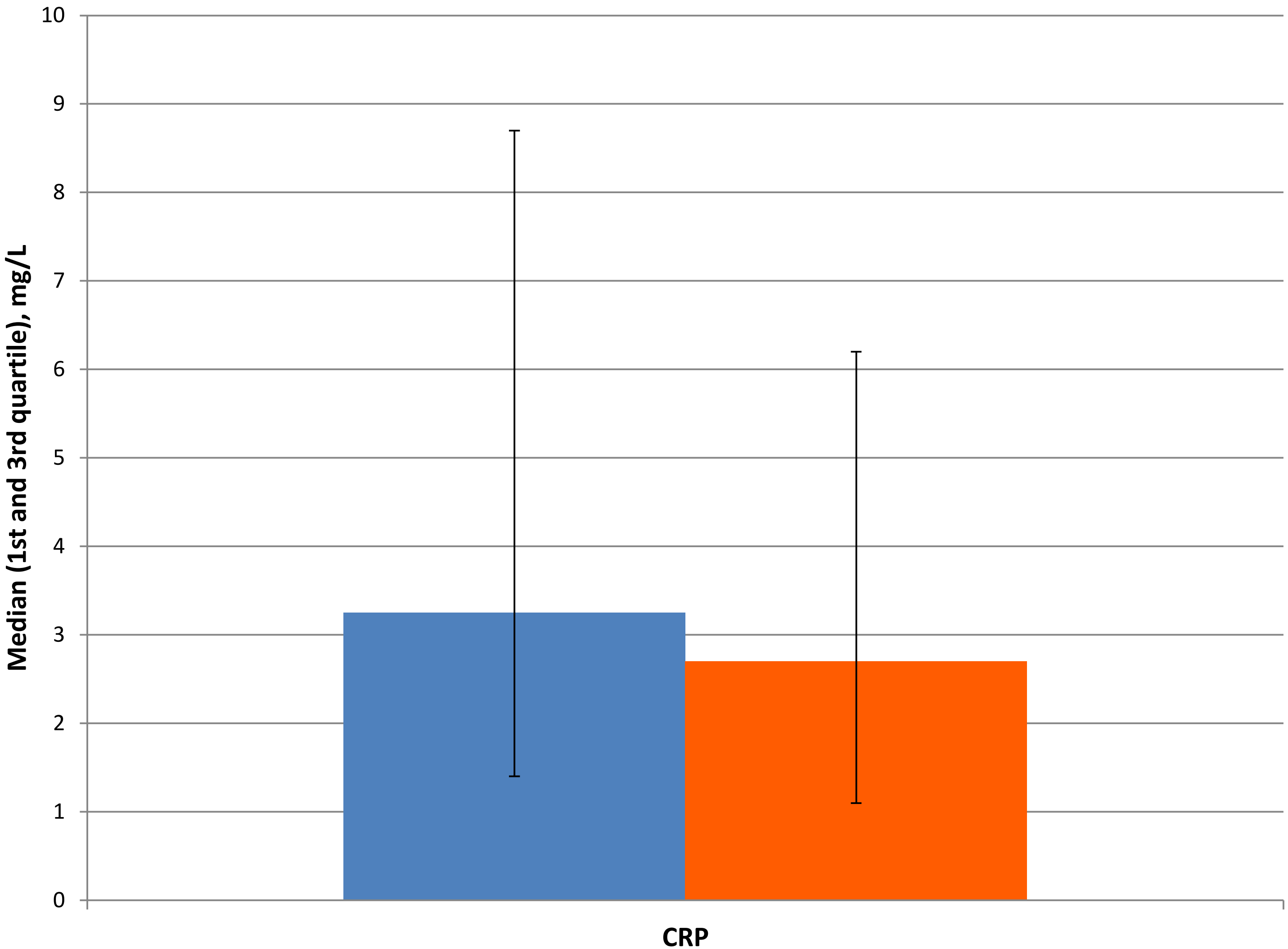
# White Cell Count




Significant difference ($p<0.05$) after adjusting for age, sex, ethnicity, HbA1c, BMI, smoking, macrovascular disease and prescribed medications

Laake JP et al
Diabetes Care 2013 75:791-7

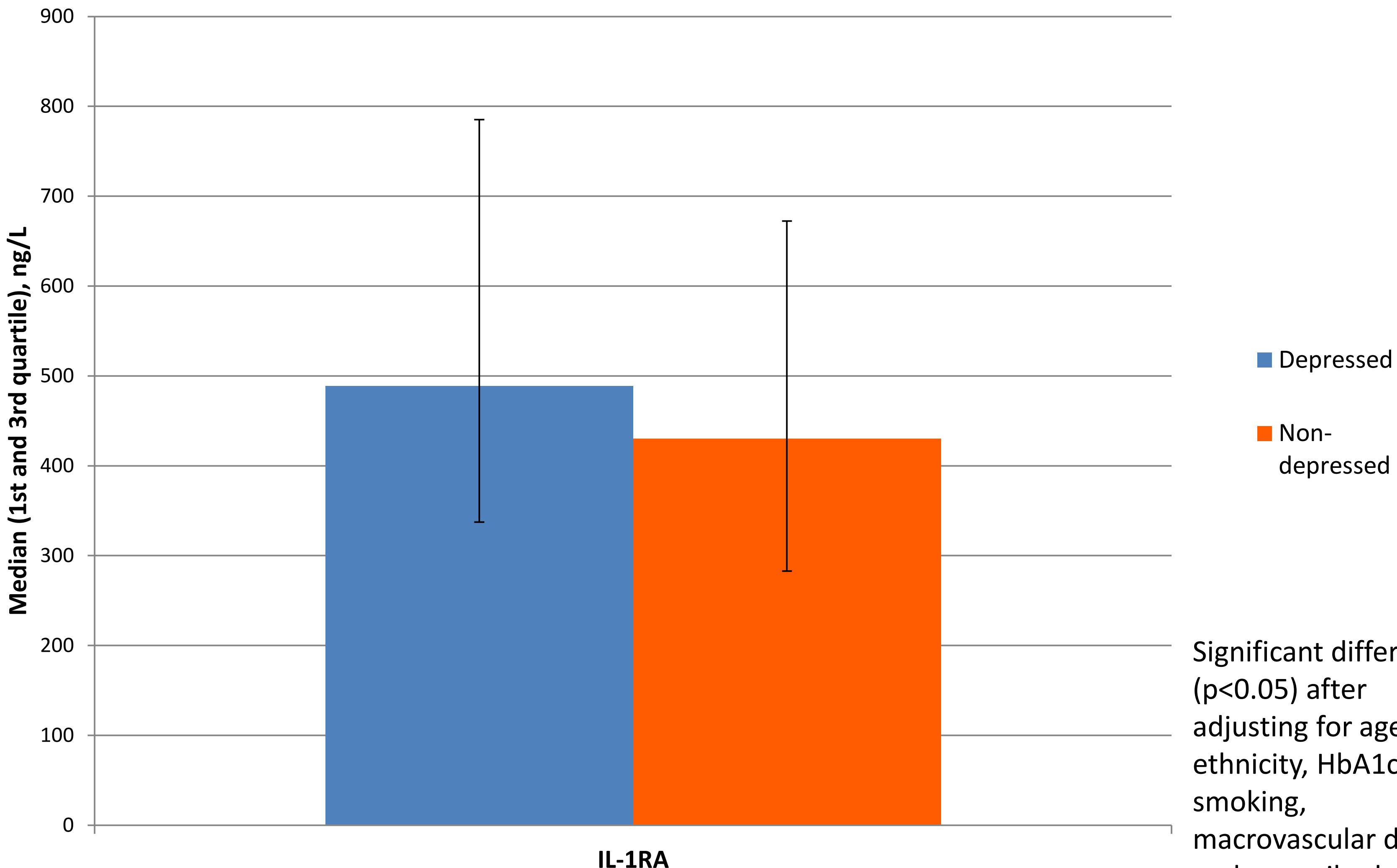
# C-reactive protein




Significant difference ($p<0.05$) after adjusting for age, sex, ethnicity, HbA1c, BMI, smoking, macrovascular disease and prescribed medications

Laake JP et al
Diabetes Care 2013 75:791-7

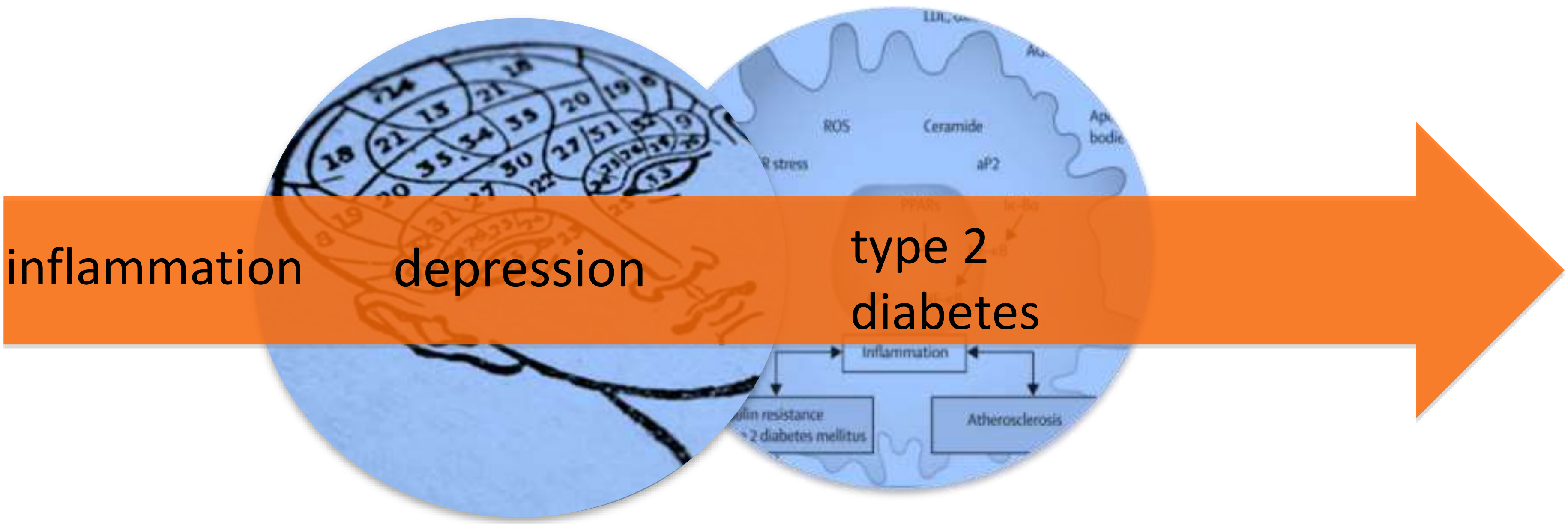
# IL-1 receptor antagonist




Significant difference ($p<0.05$) after adjusting for age, sex, ethnicity, HbA1c, BMI, smoking, macrovascular disease and prescribed medications

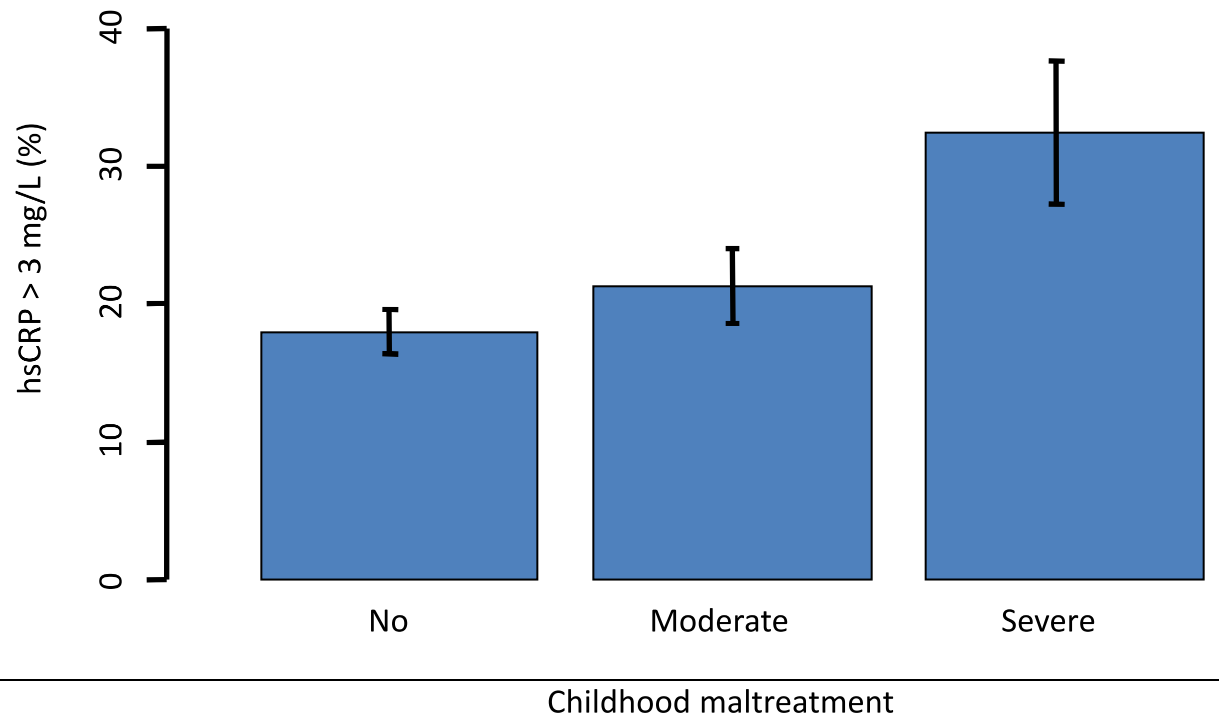
Laake JP et al
Diabetes Care 2013 75:791-7

# Depression-diabetes link=inflammation appears to be common to both



# Childhood maltreatment is associated with inflammatory markers in adults

- High CRP risk group for cardiovascular disease
- (CDC, AHA): CRP>3mg/L




Danese et al PNAS 2007

# Summary

- Depression is common and associated with worse biomedical outcomes in type 2 diabetes
- There is circumstantial evidence that depression and type 2 diabetes may have more in common than previously considered
- There is growing evidence of a common biological model, namely, activation of the innate inflammatory response

# A psychiatrist and a diabetologist working together?!