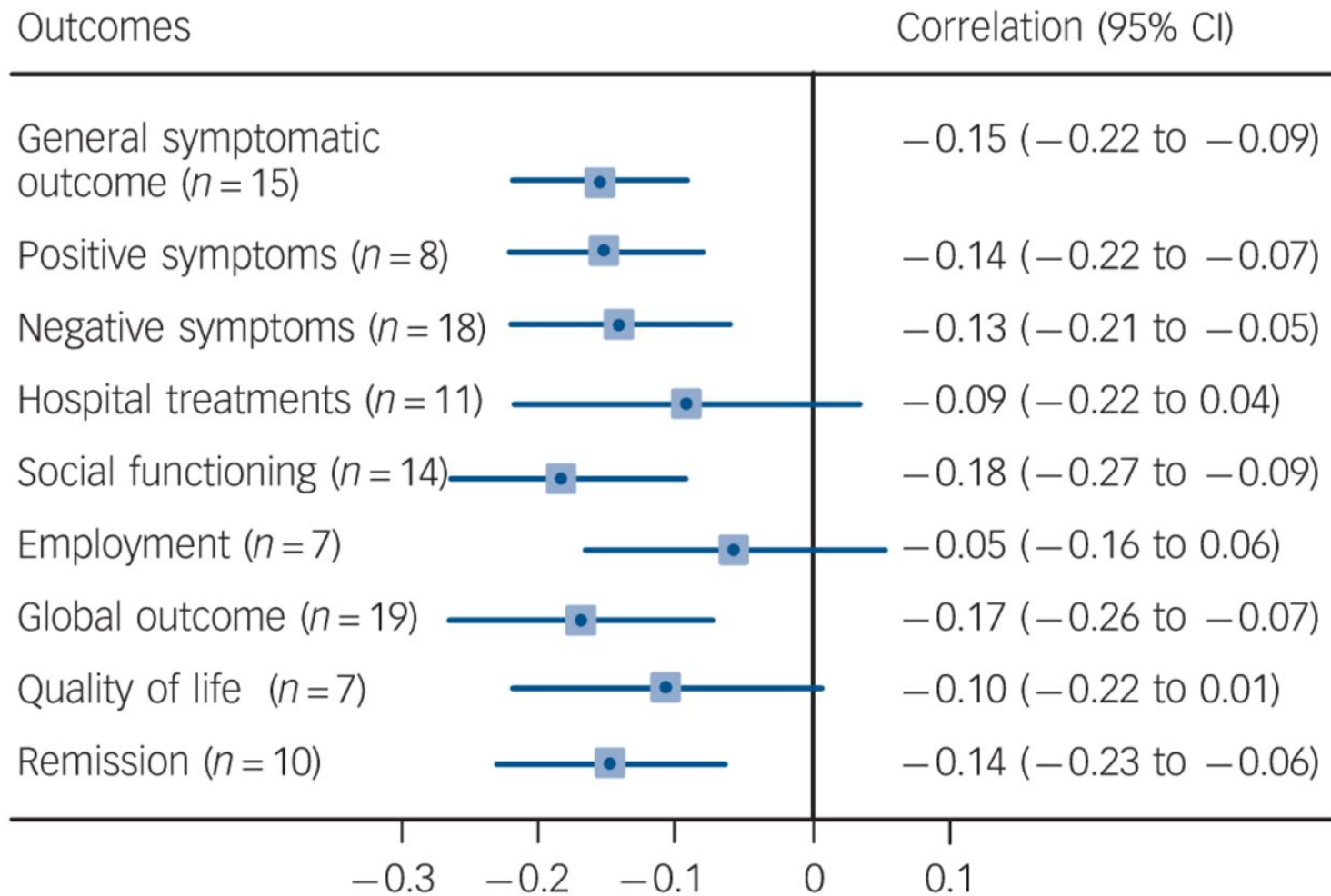


DUP: short and long term consequences

Richard Drake,
**MAHSC Clinical Lead for Mental
Health**

Correlations between duration of untreated psychosis (DUP) and clinical outcomes, hospital treatment and social functioning.

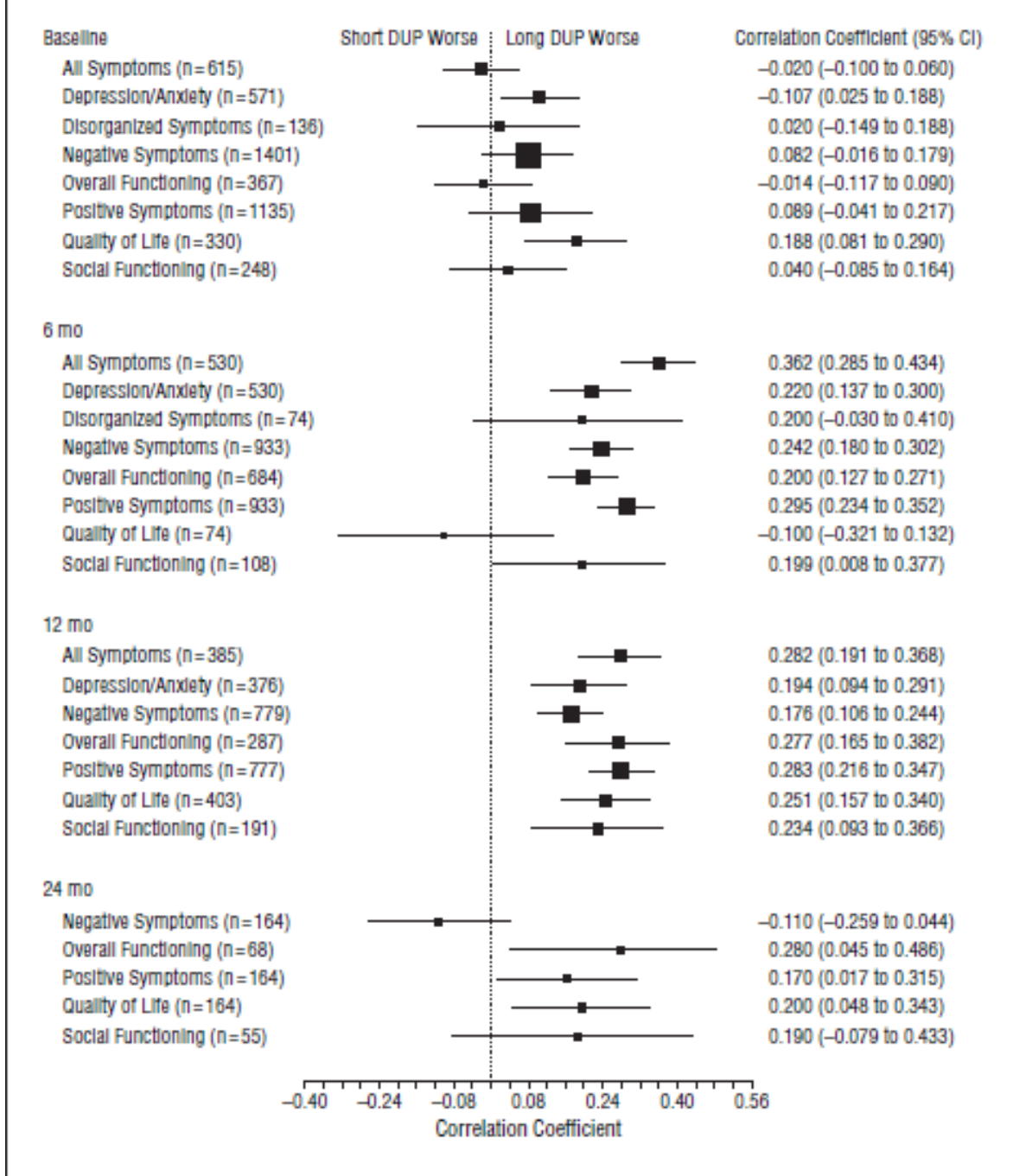


Matti Penttilä et al. *BJP* 2014;205:88-94

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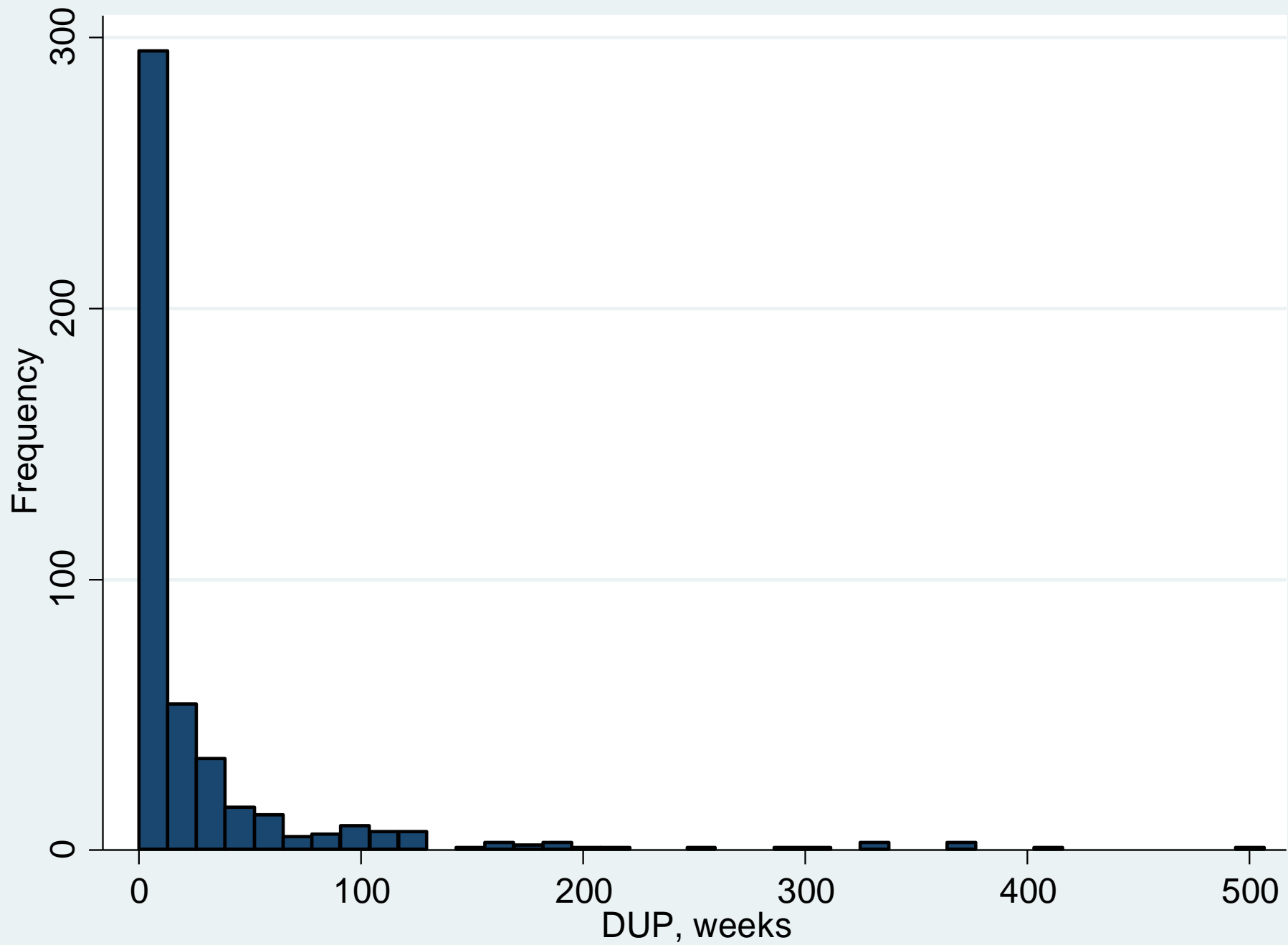
Short & long term effect on symptoms

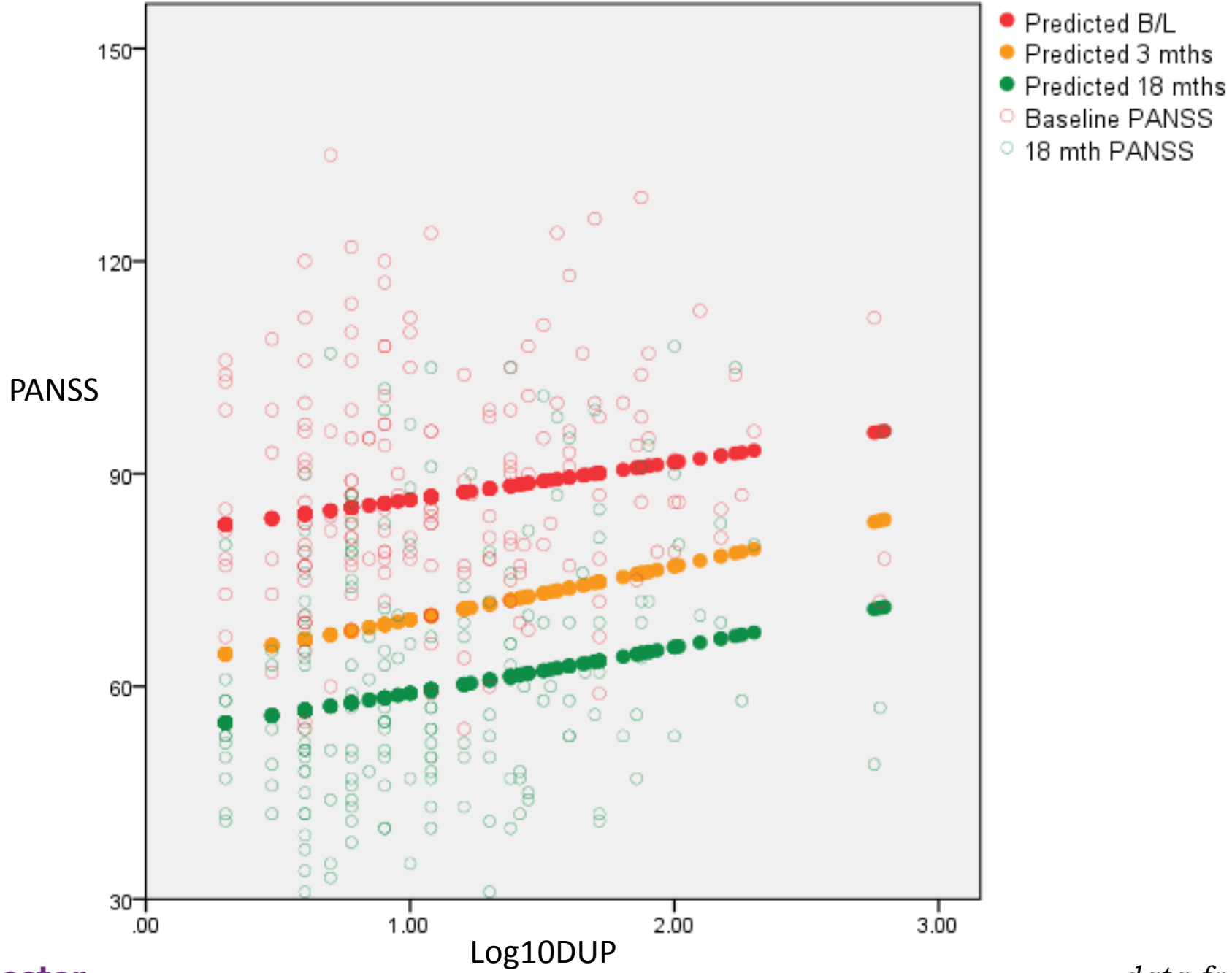
- Increasing effect over the first few months
 - Correlations increase from about $r=0.12$ to $r=0.20$

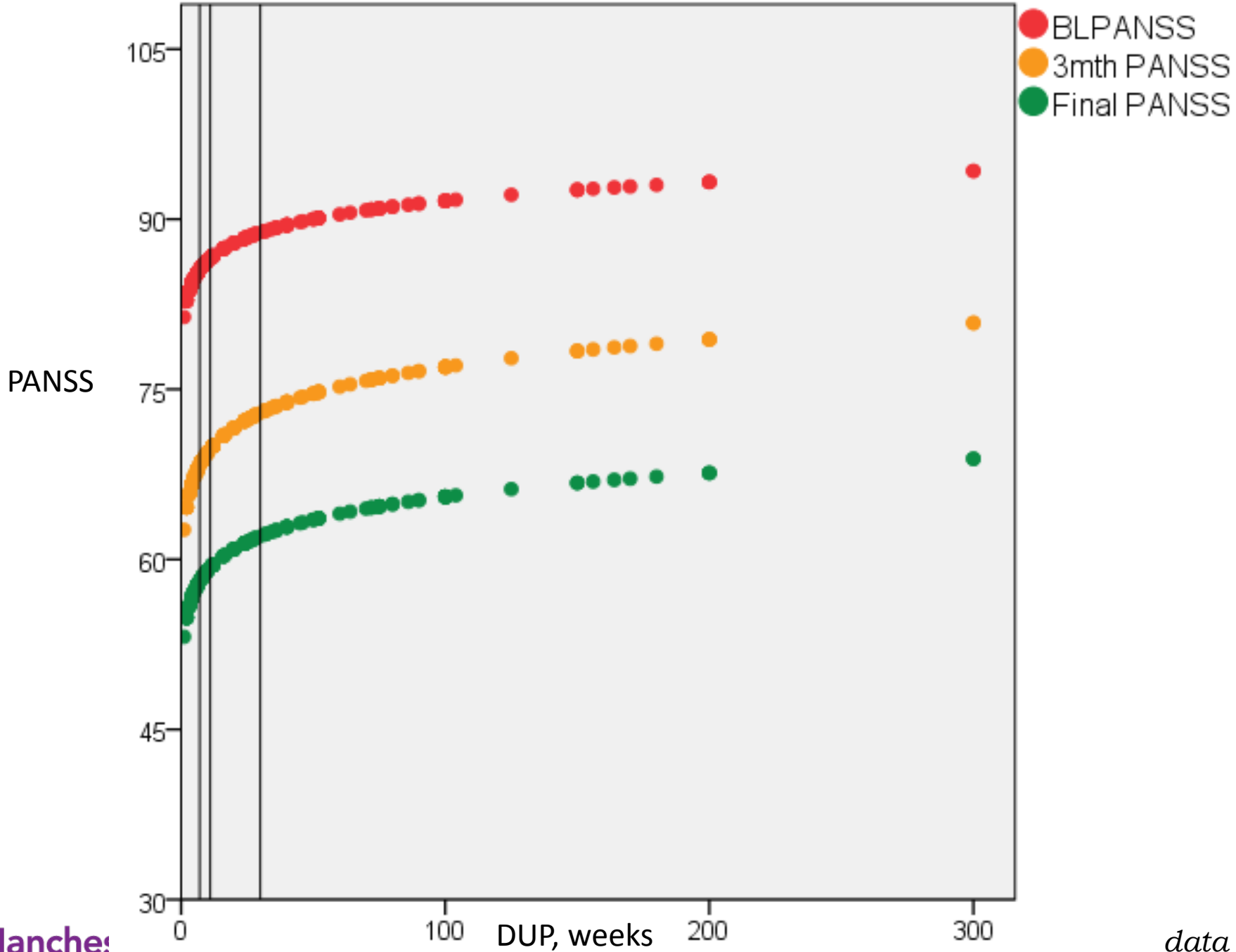


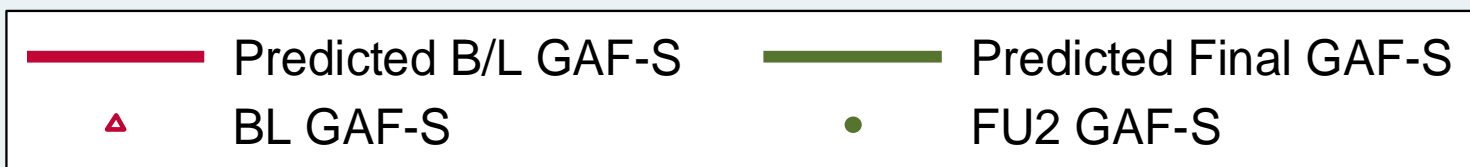
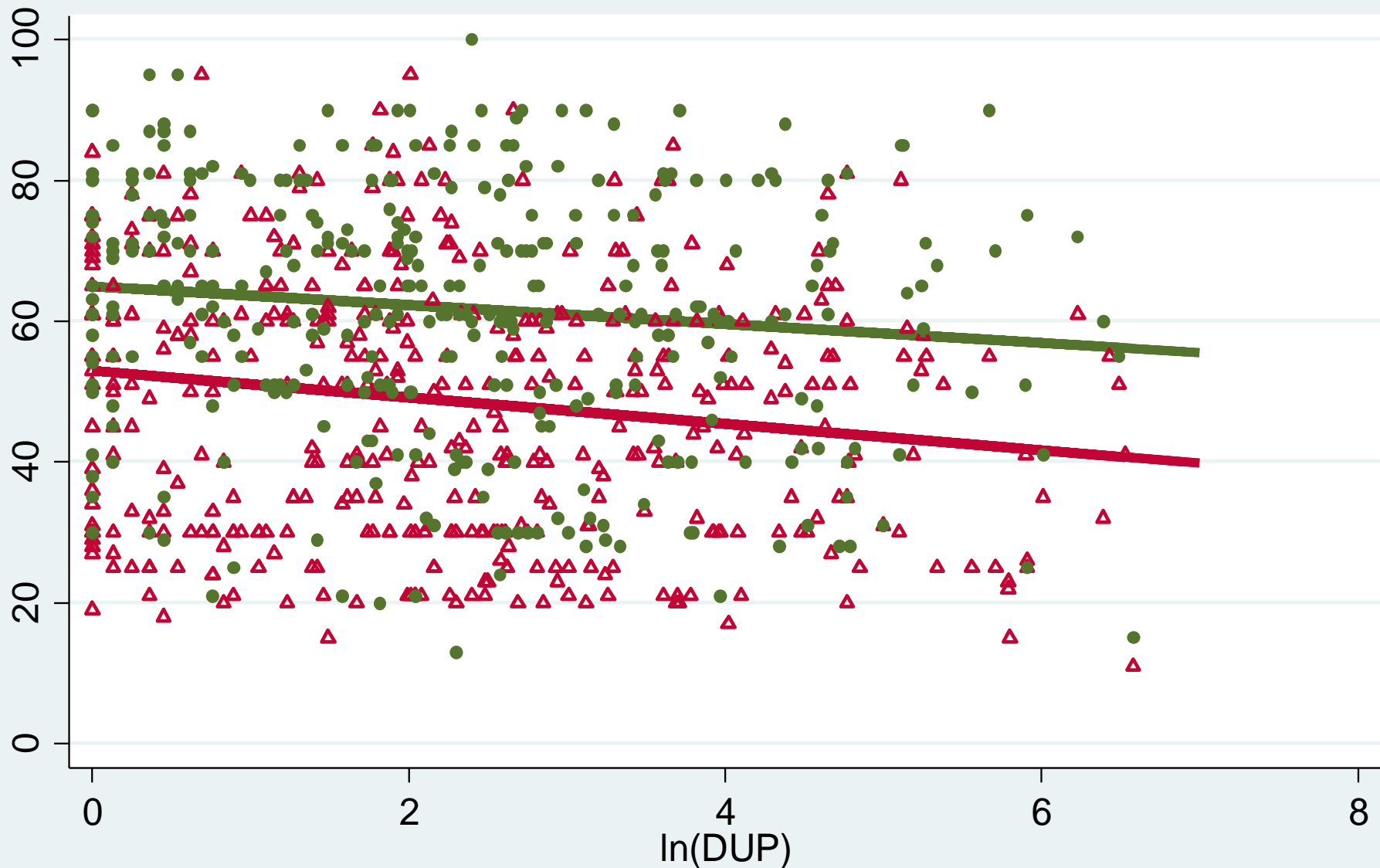
Short & long term effect on symptoms

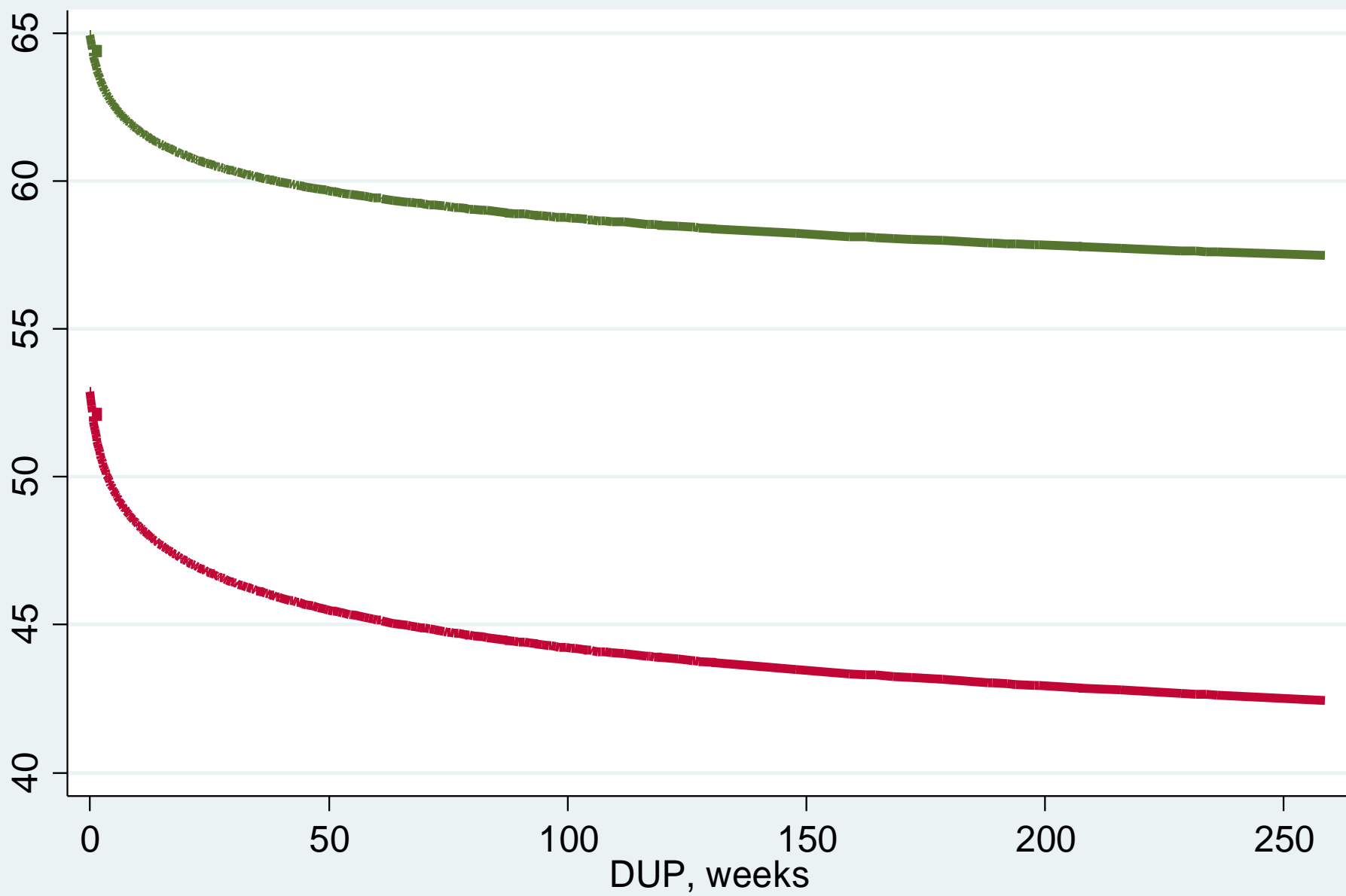
- Persisting effects over years
 - Are the effects of DUP on symptoms linear?
 - Is there a cut off for DUP's long term effects or is the effect gradual?





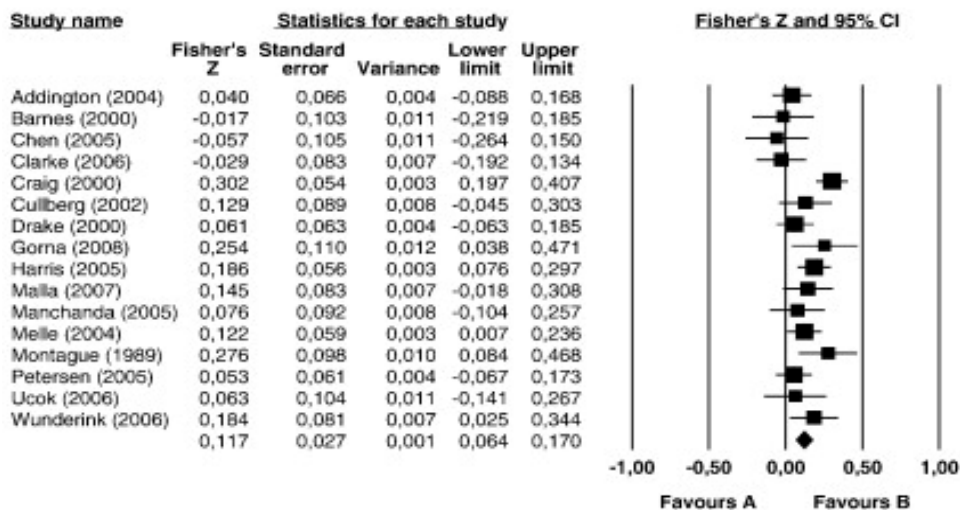




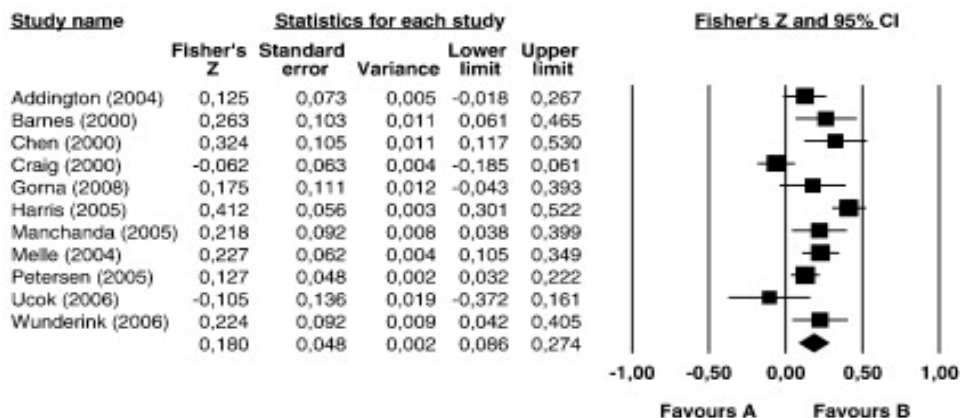


— Predicted B/L GAF-S — Predicted Final GAF-S

correlation between DUP and negative symptoms at baseline



correlation between DUP and negative symptoms at short term follow-up (1-2 year)



correlation between DUP and negative symptoms at long term follow-up (5-8 years)

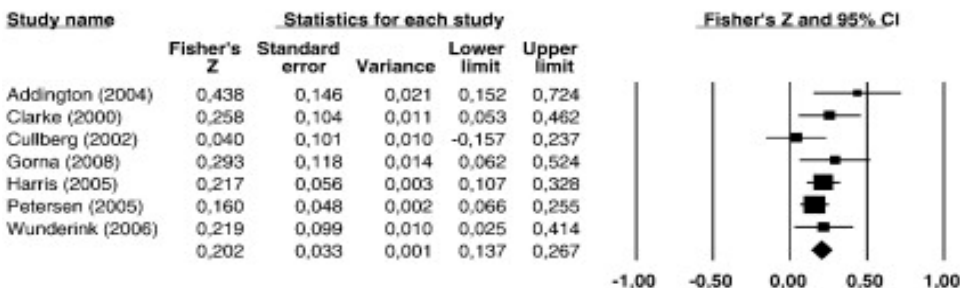


Fig. 1. Correlations between DUP and negative symptoms at baseline, after 1-2 years follow-up and after 5-8 years follow-up.
Nynke Boonstra, Rianne Klaassen, Sjoerd Sytema, Max Marshall, Lieuwe De Haan, Lex Wunderink, Durk Wiersma

Duration of untreated psychosis and negative symptoms — A systematic review and meta-analysis of individual patient data
Schizophrenia Research, Volume 142, Issues 1–3, 2012, 12–19

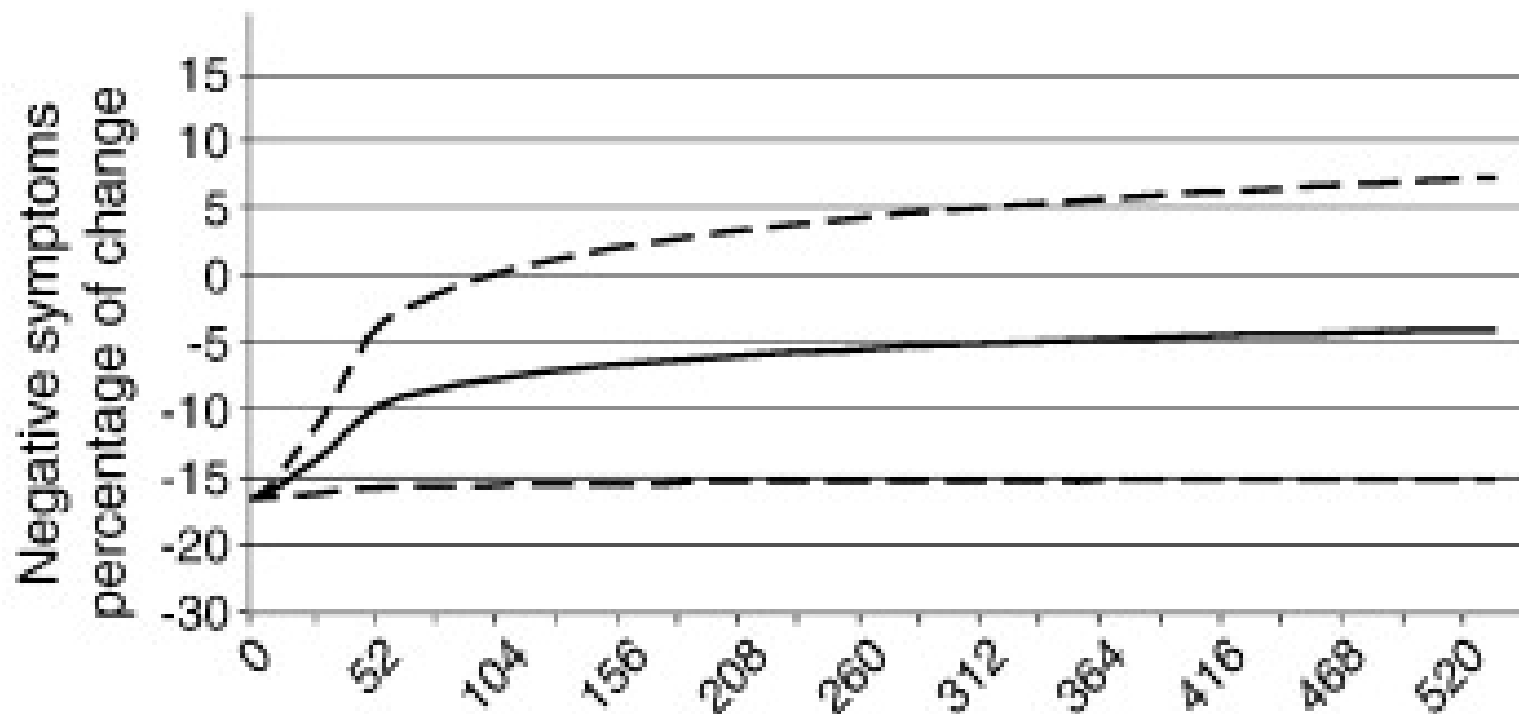


Fig. 2. Predicted change in negative symptoms after short term, follow-up (1–2 years) against duration of untreated psychosis in weeks (with 95% CIs).

Nynke Boonstra, Rianne Klaassen, Sjoerd Sytema, Max Marshall, Lieuwe De Haan, Lex Wunderink, Durk Wiersma

Duration of untreated psychosis and negative symptoms — A systematic review and meta-analysis of individual patient data

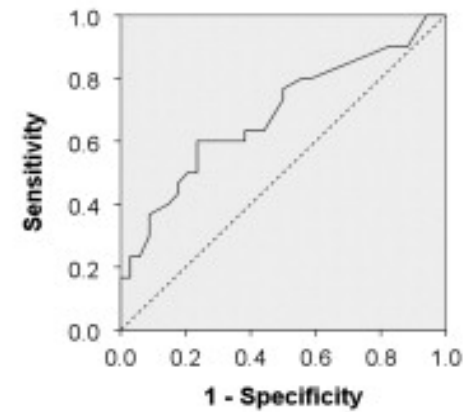
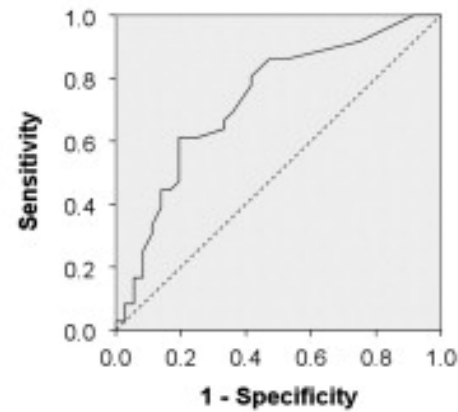
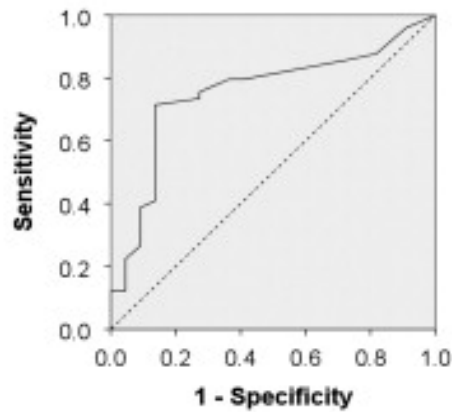
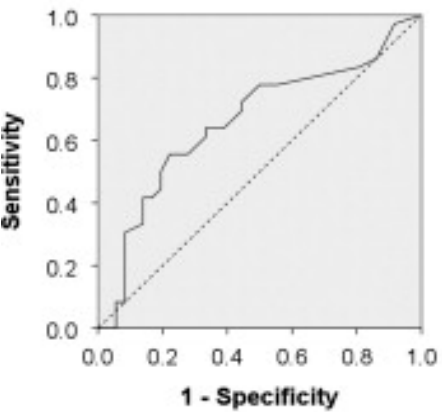
K3

K7

K12

K20

GAF over 60 pts



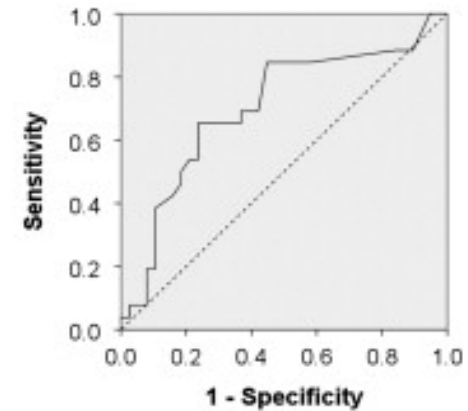
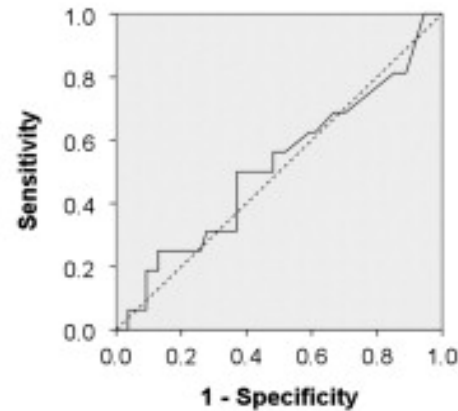
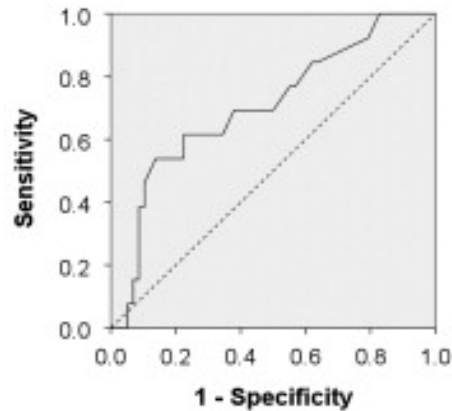
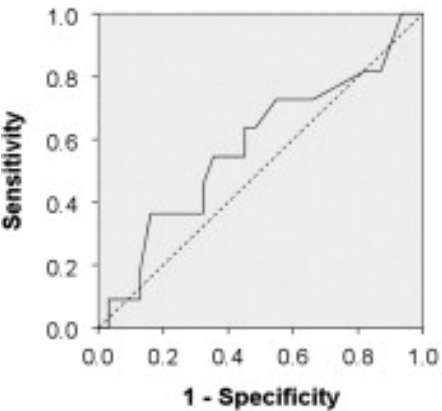
$p=0.019$
 DUP 23 weeks Sen.=0.556 1-Spc=0.222

$p=0.001$
 DUP 12.5 weeks Sen.=0.714 1-Spc=0.136

$p=0.001$
 DUP 23 weeks Sen.=0.611 1-Spc=0.194

$p=0.011$
 DUP 23 weeks Sen.=0.600 1-Spc=0.235

BPRS remission 3 pts and above



$p=0.405$

$p=0.022$
 DUP 53 weeks Sen.=0.538 1-Spc=0.138

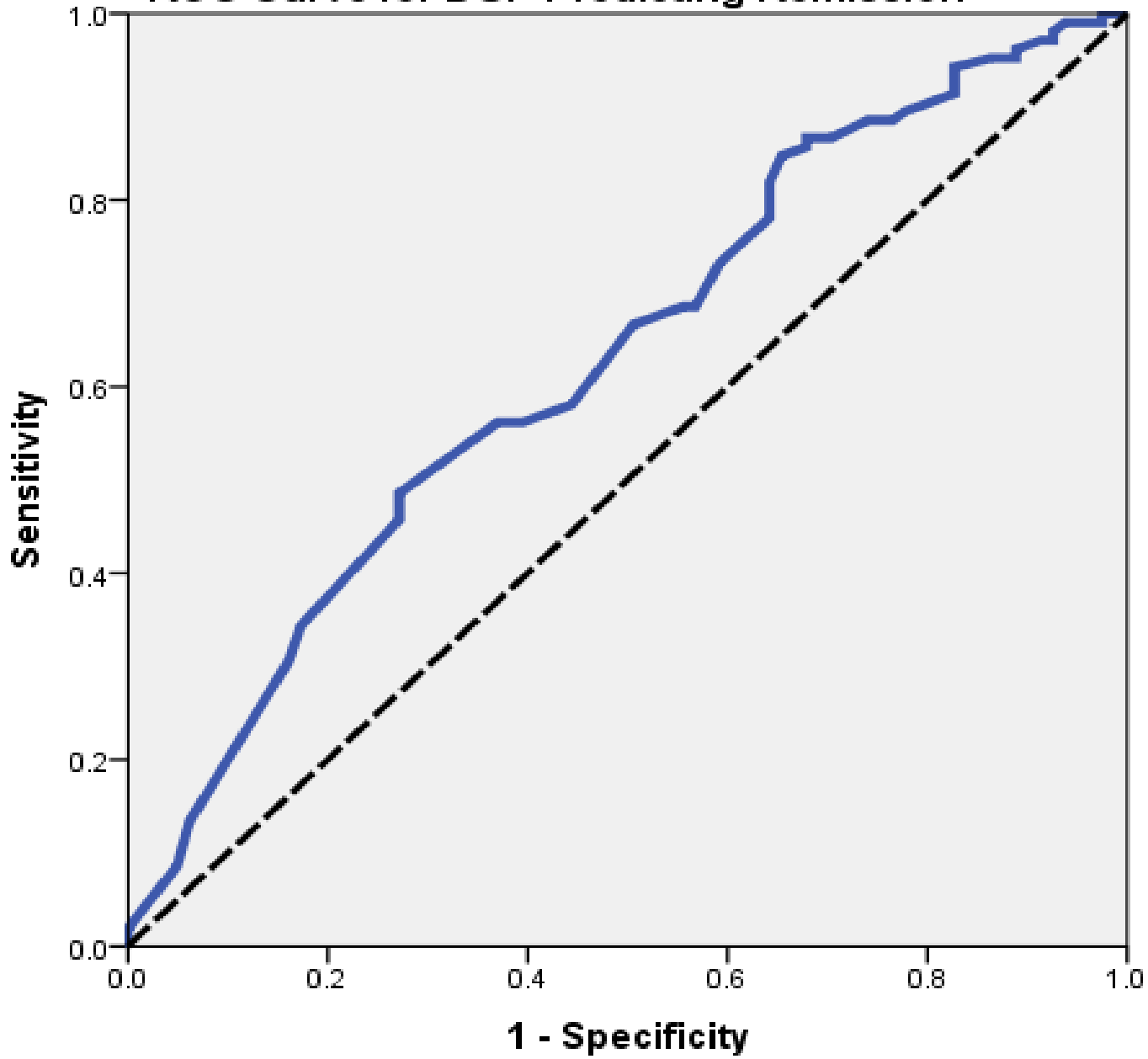
$p=0.828$

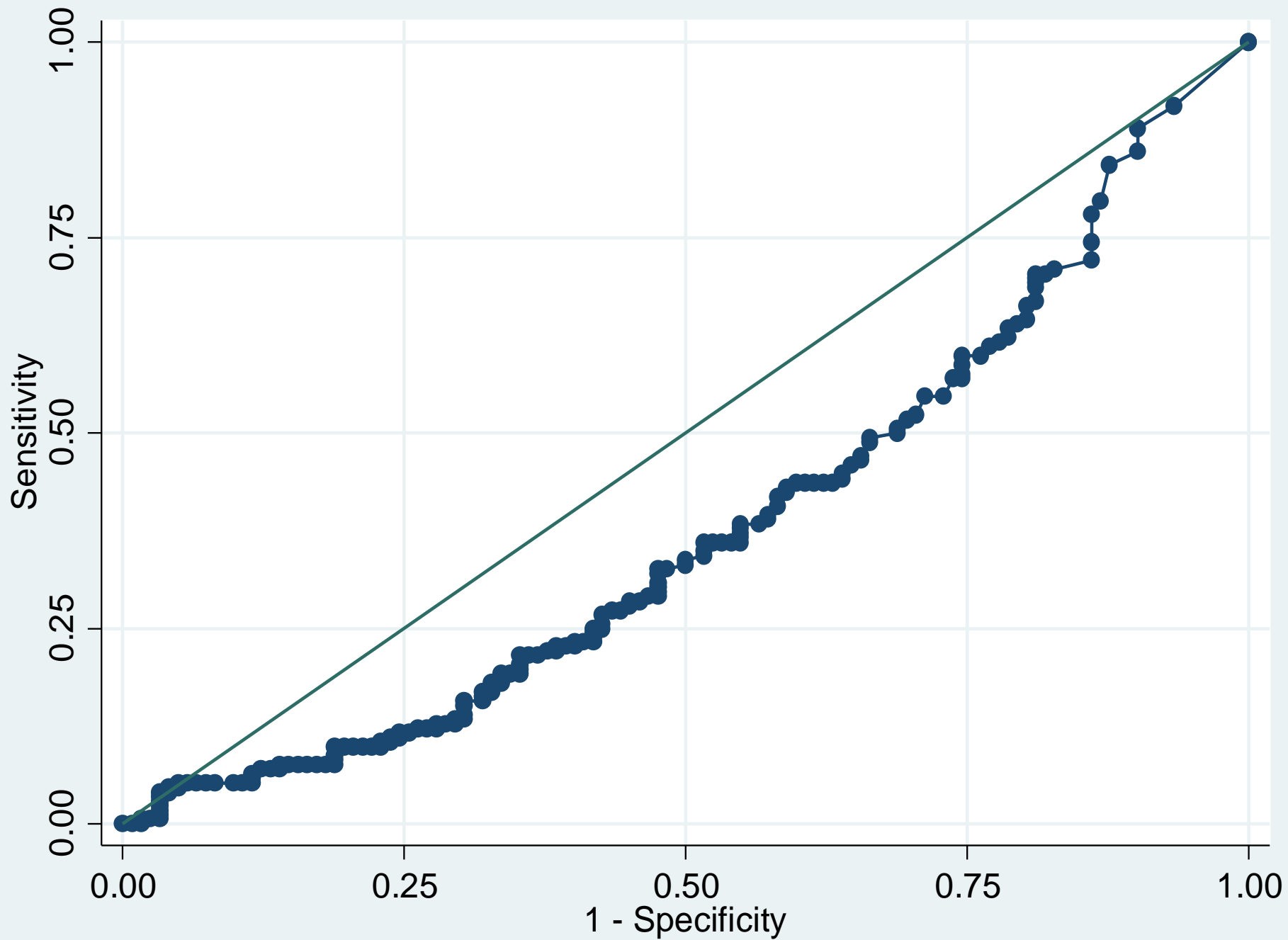
$p=0.007$
 DUP 23 weeks Sen.=0.654 1-Spc=0.237

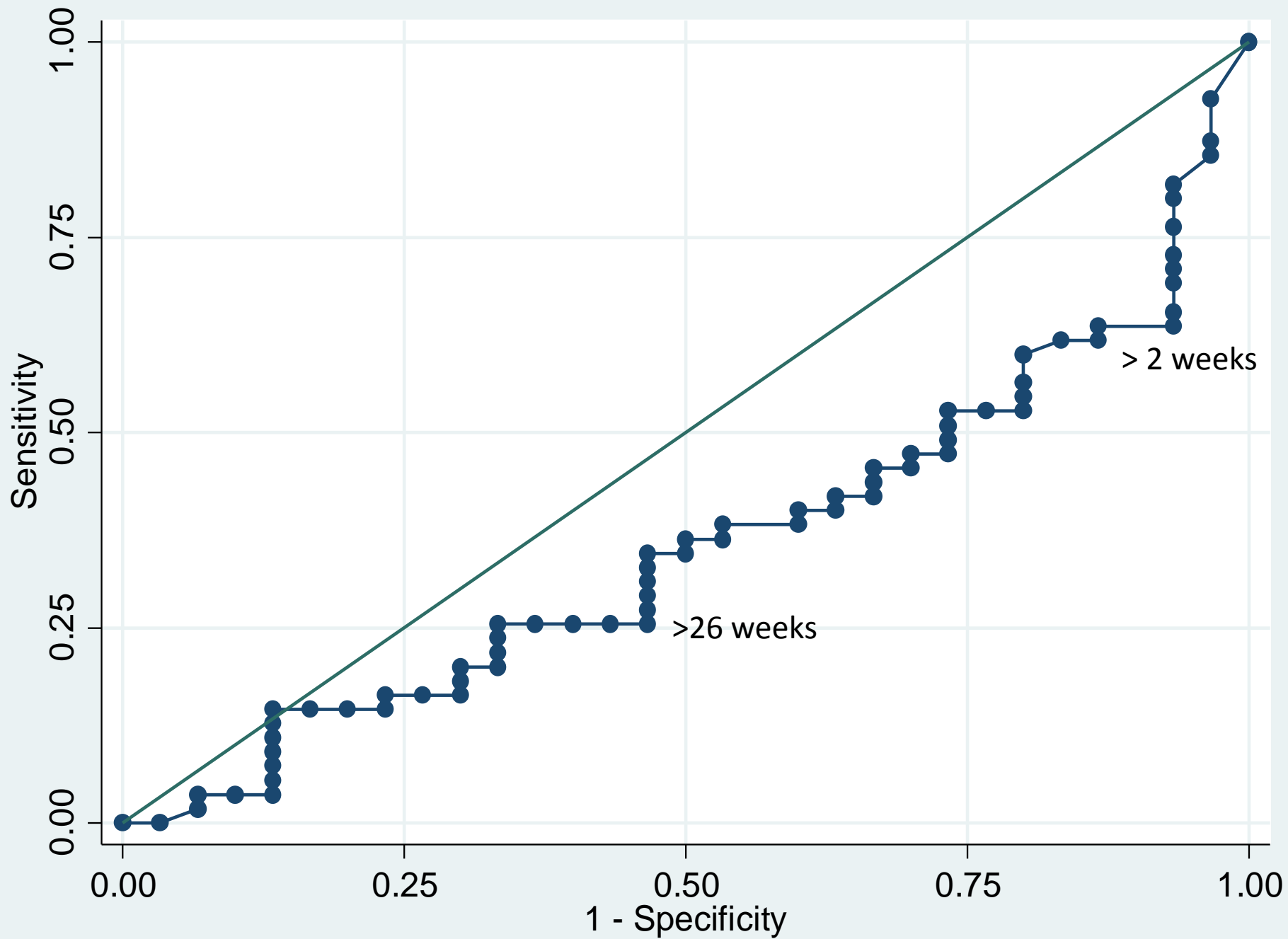
Fig. 1 The results of ROC analyses.

Andrzej Cechnicki, Łukasz Cichoński, Aneta Kalisz, Piotr Błądziński, Przemysław Adamczyk, Joanna Franczyk-Głita
 Duration of untreated psychosis (DUP) and the course of schizophrenia in a 20-year follow-up study

ROC Curve for DUP Predicting Remission







How and why does DUP predict O/C?
IT'S ALL A BIT COMPLICATED

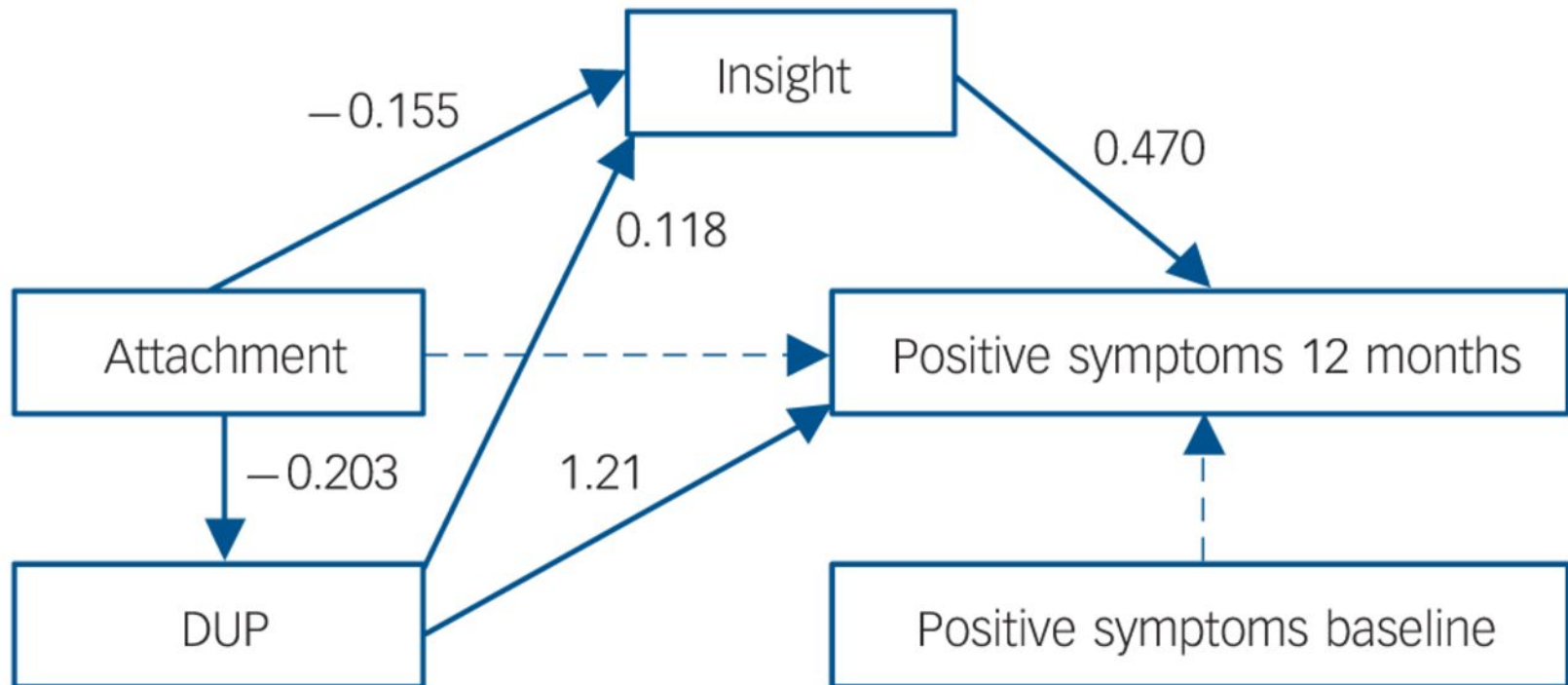
Problems relating DUP & OC

- DUP is moderately reliable
 - But is measured retrospectively
- DUP is a proxy
 - Not clear for what
 - Often for things that are hard to measure reliably
- Outcomes may be measured poorly
 - They may be affected by confounding and moderation

Predictors of long DUP

- Poor Insight
- Avolition
- Social Isolation
- Preserved ADL
- Lack of hostility

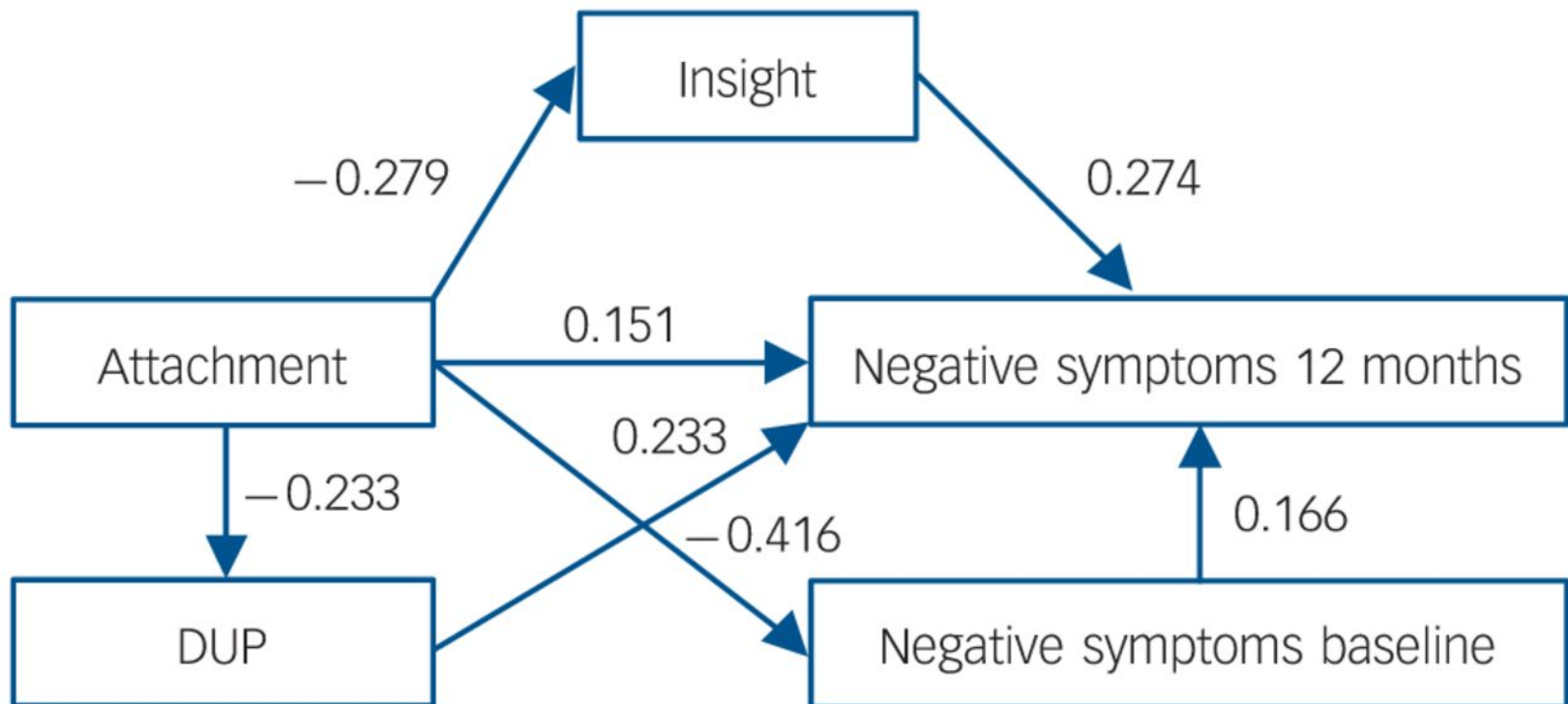
Mediation model, Positive and Negative Syndrome Scale (PANSS) positive symptoms at 12 months. $\chi^2 = 13.82$ ($P = 0.061$); robust comparative fit index (RCFI) = 0.973; root mean square of approximation (RMSEA) = 0.05.



A. I. Gumley et al. *BJP* 2014;205:60-67

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Mediation model, Positive and Negative Syndrome Scale (PANSS) negative symptoms at 12 months. $\chi^2 = 9.89$ ($P = 0.094$); robust comparative fit index (RCFI) = 0.926; root mean square of approximation (RMSEA) = 0.04.



A. I. Gumley et al. *BJP* 2014;205:60-67

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Predictors of long DUP

- Poor Insight
 - Non-medical explanatory models
- Avolition
- Social Isolation
 - Lack of family support
 - Poor Attachment
- Preserved ADL
 - Lack of purchasing power in LMIC
- Lack of Hostility

Large M et al. BJPsych 2008

Oliveira AM et al. Schiz Res 2010

Farooq S et al. Schiz Res 2010

Gumley AI et al. BJPsych 2014

Tomita A et al. JNervMentDis 2015

Confounding with poor OC

- Poor insight also predicts:
 - relapse, readmission,
 - perhaps violence over the short term
- Avolition is associated with negative symptoms that may be trait-like
- Good ADL may confound DUP's effect on SF
- Isolation & lack of support; poverty & marginalisation; hostility & delinquency may confound too

Immediate consequences

- Suicide
 - 44-57% severe DSH in Sz APS-naïve
- Violence & homicide
 - 39-41% homicides in Sz APS-naïve
 - Delinquency lengthens DUP, hostility shortens it
- Symptom progression increases risk in EIS
 - Long DUP worsens psychosis and hence violence
 - Long DUP leads psychosis & depression to persist

Nielssen OB et al JClinPsych 2012

Winsper C et al JAMA Pscyh 2013

Uptegrove R et al 2014

NCISH Annual Report 2015

Immediate consequences

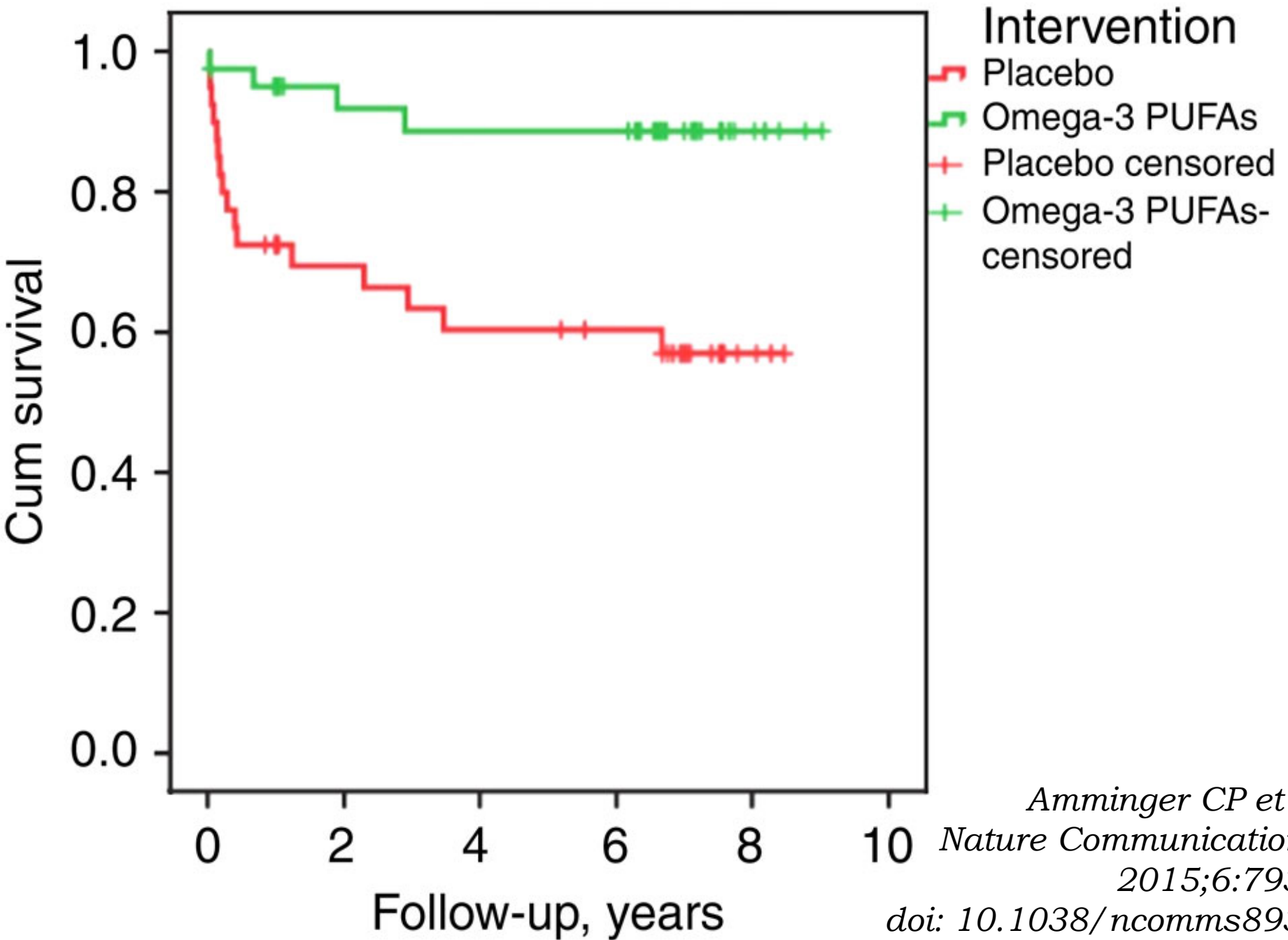
- No consistent evidence of cerebral deterioration
 - Hints of GM loss, e.g. temporal gyri, fusiform/lingual gyrus, planum temporale
 - Inconsistent changes in frontal & BG volume
 - Hints of NC deficits, e.g. verbal, prospective memory; IQ; set shifting
- Better evidence of GM loss after and NC deterioration before this period

Long term: Treatment delay

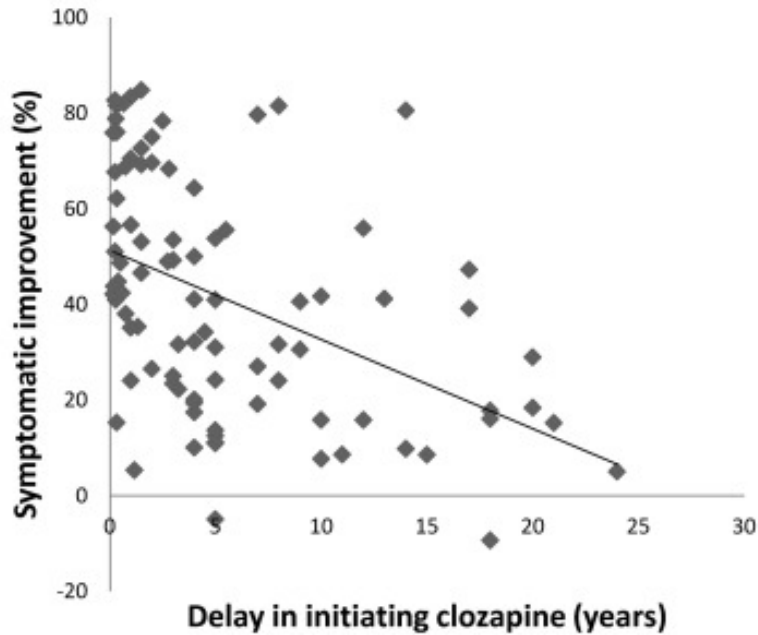
- Early intervention with 3/12 Ω 3-PUFAs
 - Benefits 7-8y on
- Late response to treatment
 - Low IQ 10 years on
- Late starting of CLZ
 - Effect up to 25 years on

Amminger CP et al 2015
Barder HE et al Psychiatr Res
2015;225:515–521
Yada Y et al 2015

Survival functions



(a) BPRS total score



(b) BPRS psychosis score

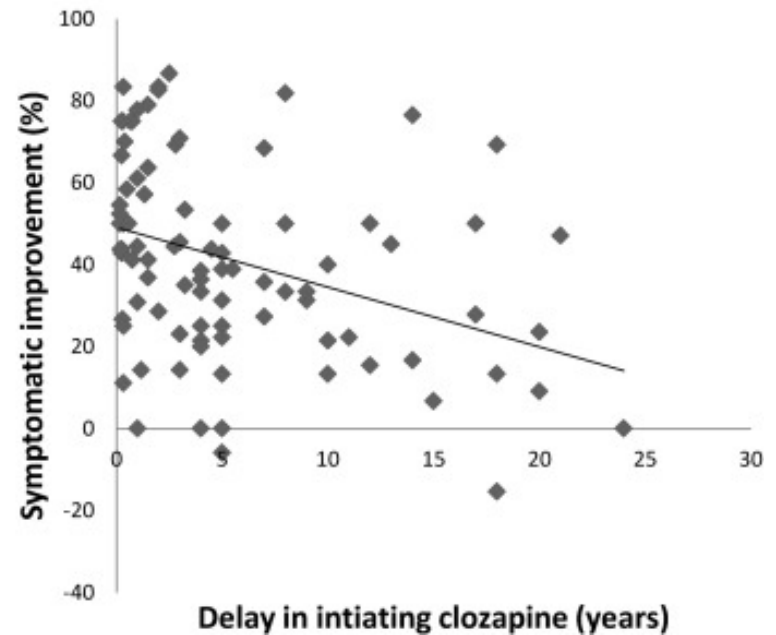


Fig. 1. The correlations between improvement in the 18-item Brief Psychiatric Rating Scale (BPRS) total/psychosis scores at last observation and delay in initiating clozapine (DIC) were analyzed using Spearman's rank correlation coefficient.(a) Long DIC correl...

Yuji Yada, Bunta Yoshimura, Yoshiki Kishi

Correlation between delay in initiating clozapine and symptomatic improvement

Schizophrenia Research, Volume 168, Issues 1–2, 2015, 585–586

<http://dx.doi.org/10.1016/j.schres.2015.07.045>

Summary

- There can be mayhem during the untreated period
- There is little evidence linking untreated psychosis to neuronal loss; maybe temporal?
- DUP's effect on symptoms is curvilinear
- DUP predicts treatment response, but should be considered with response delay as a predictor