Using Trial data to test the proposed 5 diabetes subgroups from cluster analysis

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Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables

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Summary

Background Diabetes is presently classified into two main forms, type 1 and type 2 diabetes, but type 2 diabetes in particular is highly heterogeneous. A refined classification could provide a powerful tool to individualise treatment regimens and identify individuals with increased risk of complications at diagnosis.

Methods We did data-driven cluster analysis (k-means and hierarchical clustering) in patients with newly diagnosed diabetes (n=8980) from the Swedish All New Diabetics in Scania cohort. Clusters were based on six variables (glutamate decarboxylase antibodies, age at diagnosis, BMI, HbA_{1c}, and homoeostatic model assessment 2 estimates of β-cell function and insulin resistance), and were related to prospective data from patient records on development of complications and prescription of medication. Replication was done in three independent cohorts: the Scania Diabetes Registry (n=1466), All New Diabetics in Uppsala (n=844), and Diabetes Registry Vaasa (n=3485). Cox regression and logistic regression were used to compare time to medication, time to reaching the treatment goal, and risk of diabetic complications and genetic associations.

Findings We identified five replicable clusters of patients with diabetes, which had significantly different patient characteristics and risk of diabetic complications. In particular, individuals in cluster 3 (most resistant to insulin) had significantly higher risk of diabetic kidney disease than individuals in clusters 4 and 5, but had been prescribed similar diabetes treatment. Cluster 2 (insulin deficient) had the highest risk of retinopathy. In support of the clustering, genetic associations in the clusters differed from those seen in traditional type 2 diabetes.

Interpretation We stratified patients into five subgroups with differing disease progression and risk of diabetic complications. This new substratification might eventually help to tailor and target early treatment to patients who would benefit most, thereby representing a first step towards precision medicine in diabetes.

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Type 2 diabetes varies greatly but are there 5 subtypes?

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Emma Ahlqvist et al.
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Diabetes is actually five separate diseases, research suggests

By James Gallagher
Health and science correspondent, BBC News
2 March 2018
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The Guardian

Five categories for adult diabetes, not just type 1 and type 2, study shows

Findings shed light on variations in response to treatment between diabetics –and could help identify those at high risk of complications

5 reproducible subgroups (1 autoimmune, 4 type 2 diabetes)

Based on Swedish **registry** data:

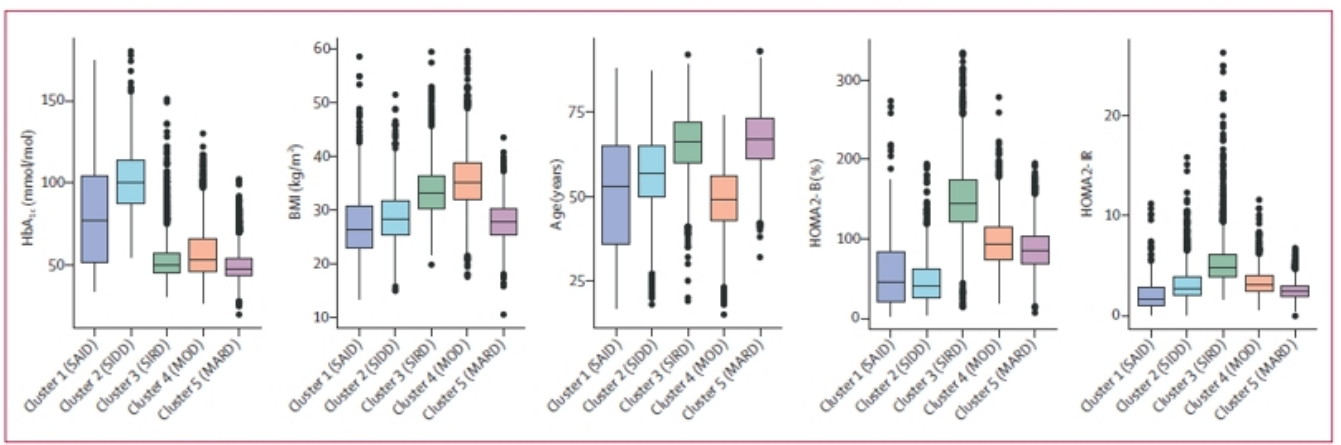


Figure 2: Cluster characteristics in the ANDIS cohort

+ GAD

From a letter to Lancet on the original article:

“...the same six variables (…) could have been used to predict outcomes at the precise combination of values for each patient, which would almost certainly be more informative and more personalized than treating the patients homogeneously within each cluster.”

Smeden, Harrell & Dahly
(Lancet diabetes-endocrinology, June 2018)

Aims – use clinical trial data to evaluate:

1) Are the 5 subgroups reproducible?
2) Do the subgroups identify patients more likely to progress, and develop complications?
3) Can the subgroups help predict drug response?
4) Do simple clinical variables (e.g. age at diagnosis, Sex, BMI, baseline HbA1c) predict outcomes better than subgroups?

Methods – use of clinical trial data

ClinicalStudy DataRequest.com

ADOPT RCT - 4,127 participants randomised to Metformin, SU or TZD

- Newly diagnosed, treatment naïve
- Age at diagnosis 56, BMI 32, baseline HbA1c 57, 58% Male
- Baseline measures of fasting C-peptide, glucose => HOMA, and GAD (N 3,802 / 4,127)
- Exclusions: renal impairment eGFR < 60, FPG < 10mmol/L
- Well measured - HbA1c, renal function up to 5 years

Analysis

1) Replication: Define subgroups – same clustering method (K-means)

2) Patient outcomes

a) Between subgroups - HbA1c progression > 1 year: mixed effect models

b) Between subgroups - time to eGFR <60

3) Are subgroups better than clinical features to predict outcomes?

Results (1) Clusters have similar characteristics in both datasets

Ahlqvist et al. (routine data) n=8,980

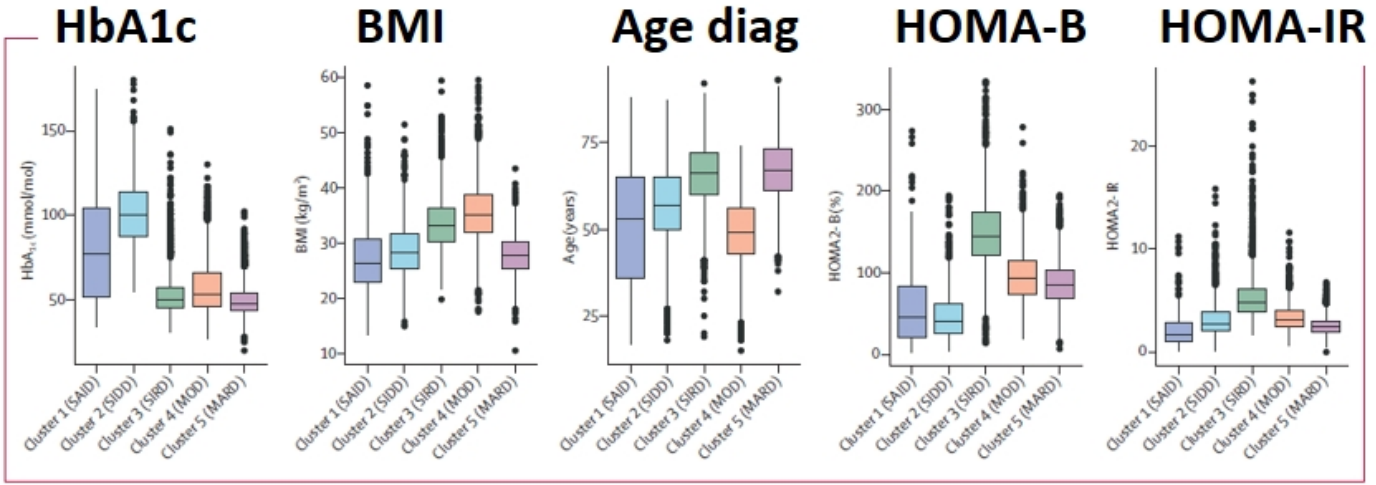
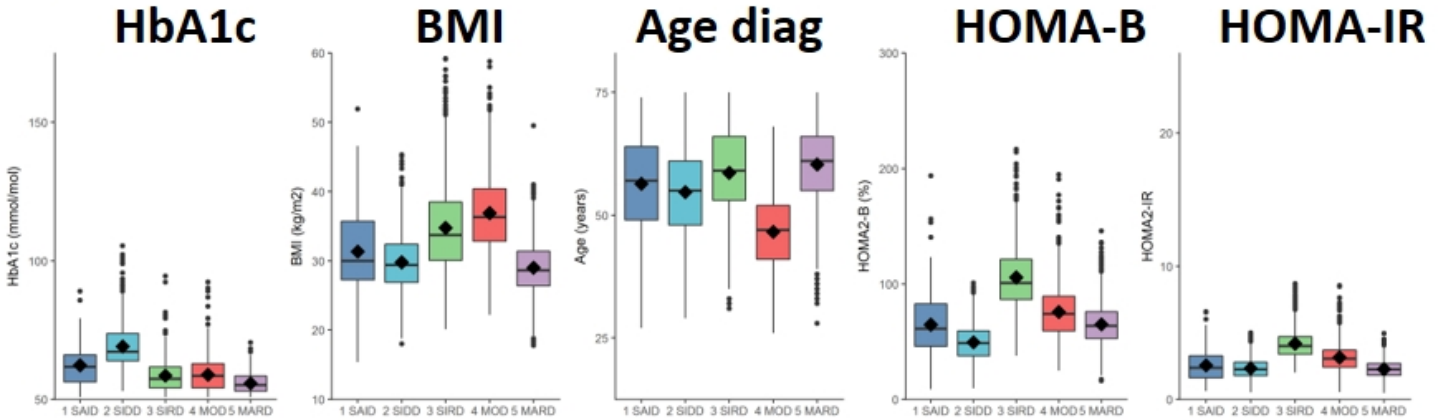


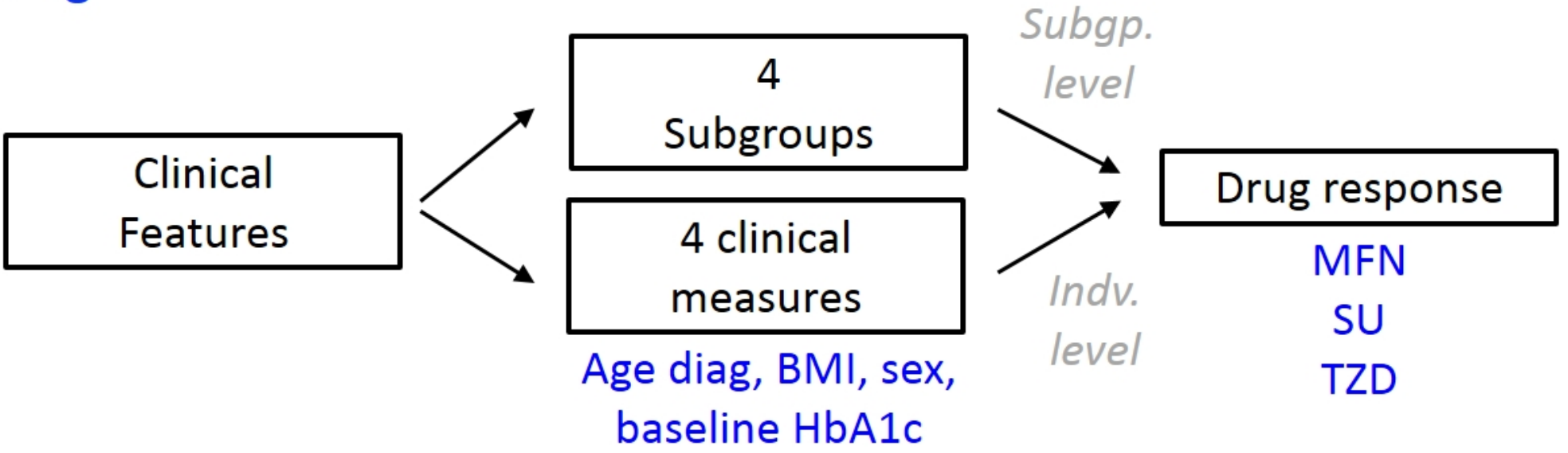
Figure 2: Cluster characteristics in the ANDIS cohort

ADOPT (trial data) n=3,802



K-means clustering

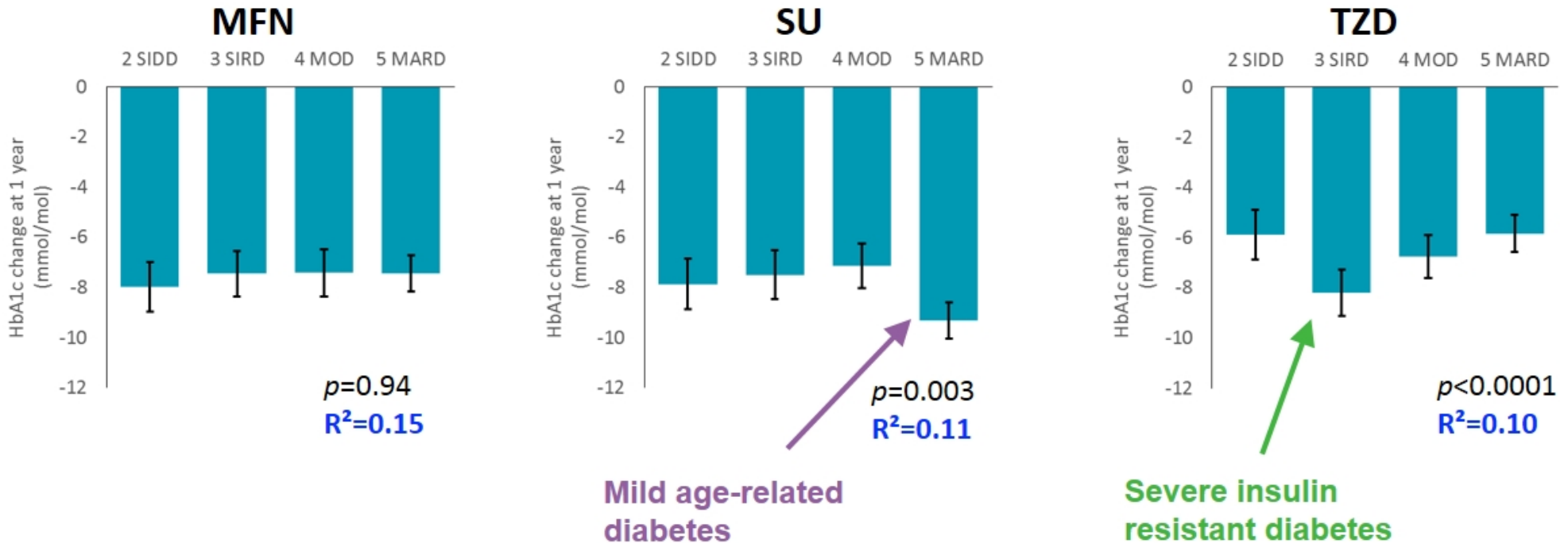
Can the subgroups help predict glycaemic response to a specific drug?



- Do the subgroups differ in 12m HbA1c response to the 3 drugs?
- Are clusters more useful than **combining 4 simple clinical measures** to make predictions for individual patients?

Results (4): 1 year glycaemic response does differ by subgroup for SU and TZD but not MFN therapy

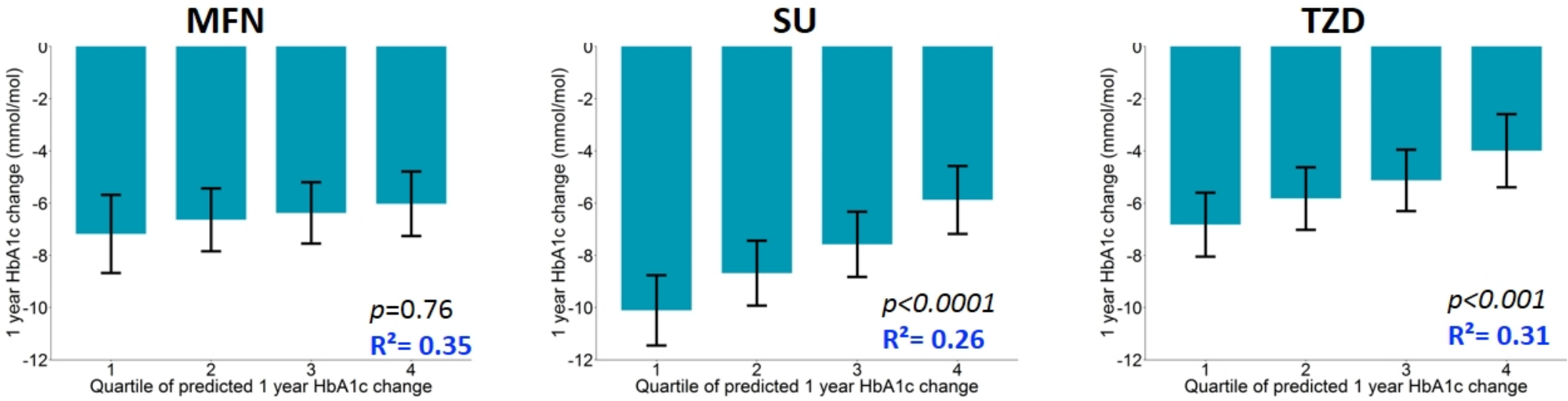
1 year HbA1c response by subgroup



N=3,515. Estimates are standardised to baseline HbA1c 57 mmol/mol

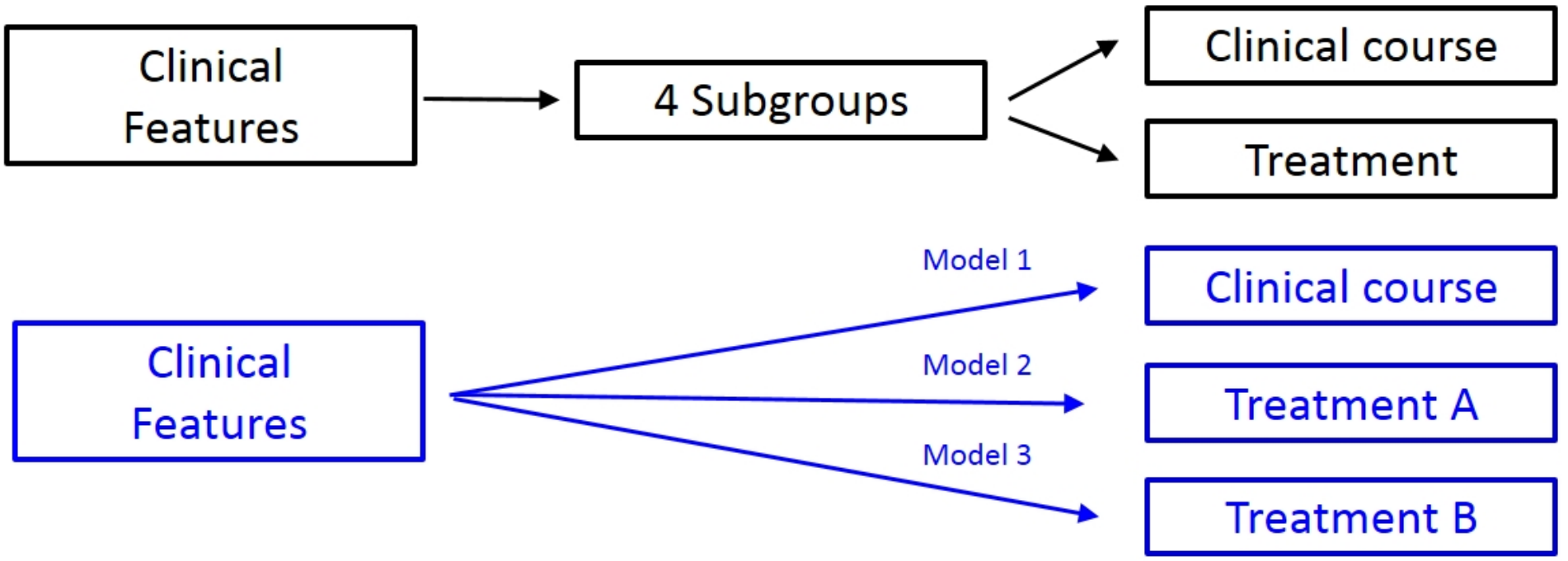
Results (4): Continuous measures can better discriminate differences in 1 year glycaemic response than subgroups

Quartiles of 1 year HbA1c response



N=3,515. Estimates are standardised to baseline HbA1c 57 mmol/mol

Conclusions



Continuous clinical measures to **predict specific outcomes for an individual** are likely to outperform subgroups

Conclusion

- It is better to use accurate measurements than grouped
- ...even if the groups are constructed by complicated algorithms
- Daily practice at SDCC: it is not a good idea to assume that persons with BMI 25.1 and 29.9 are more similar than persons with BMI 29.9 and 30.1
- ...we used BMI in groups <20, 20-25, 25-30 and 30+
- Did you?