Introduction

- NAFLD and its progressive subtype NASH have emerged as a leading indication for liver transplantation and, fueled by the obesity epidemic, as an alarmingly increasing threat to public health worldwide.
- To date, there are no approved drug therapies for NAFLD/NASH. Drug development has been challenged by the complex, 'multi-hit' pathophysiology of NAFLD, inconsistent diagnostic criteria and lack of clarity about treatment endpoints [1,2].
- NASH diagnosis and clinical trial endpoints heavily rely on liver biopsies and histological scores, e.g. the NAFLD activity score (NAS; Fig. 3a) or the fibrosis stage [3].
- Our objective was to enhance the understanding of disease processes underlying NAFLD and to assess the role of different histological and non-invasive markers in assessing NAFLD severity by using item response theory (IRT) modeling.

Methods

- The study population (n=914) originated from the public NIDDK NAFLD Adult Database [4] and spanned the full spectrum of NAFLD (NAS 0-8; Fig. 1: 52.3% with NASH).
- We developed an IRT model (using R3.6.1/mirt [5]), relating the probability of the outcome of each item (i.e. histological score) to latent variables (LV), which represent 'hidden' disease processes underlying the item responses (Fig. 3a).
- Covariates predicting NAFLD activity were identified using full random effects modeling (FREM, Psn 4.10.0 [6]), followed by a bootstrap (n=100 samples).
- Diverse types of covariates were screened (Fig. 2). Covariates were selected for final FREM (Fig. 4) if the mean expected scores corresponding to their 2.5% and 97.5% percentile spanned ±25% of the NAS or fibrosis score.

Perspectives

- The model lays the basis for future investigations, e.g. on the sensitivity of the NAS to changes of different disease processes (e.g. as response to a therapeutic intervention)—with the ultimate goal to support model-informed drug development.

References