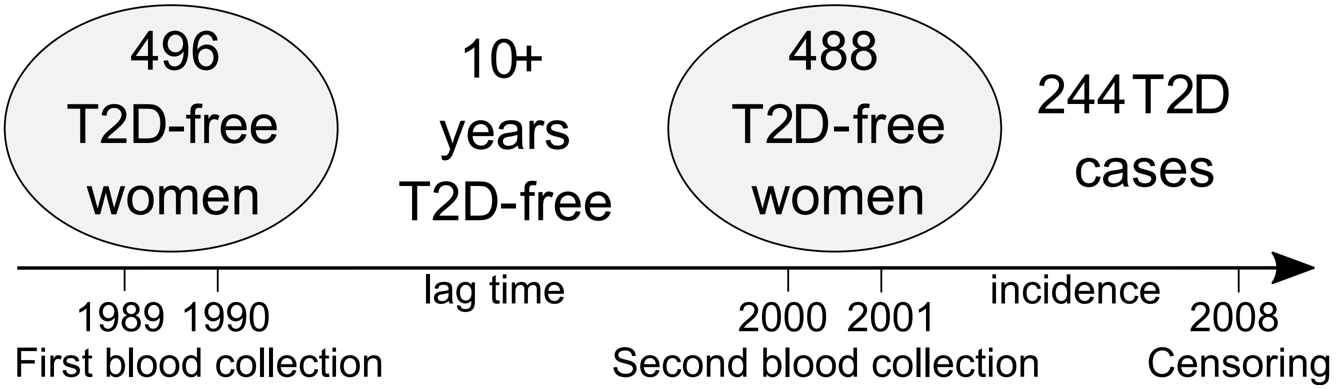
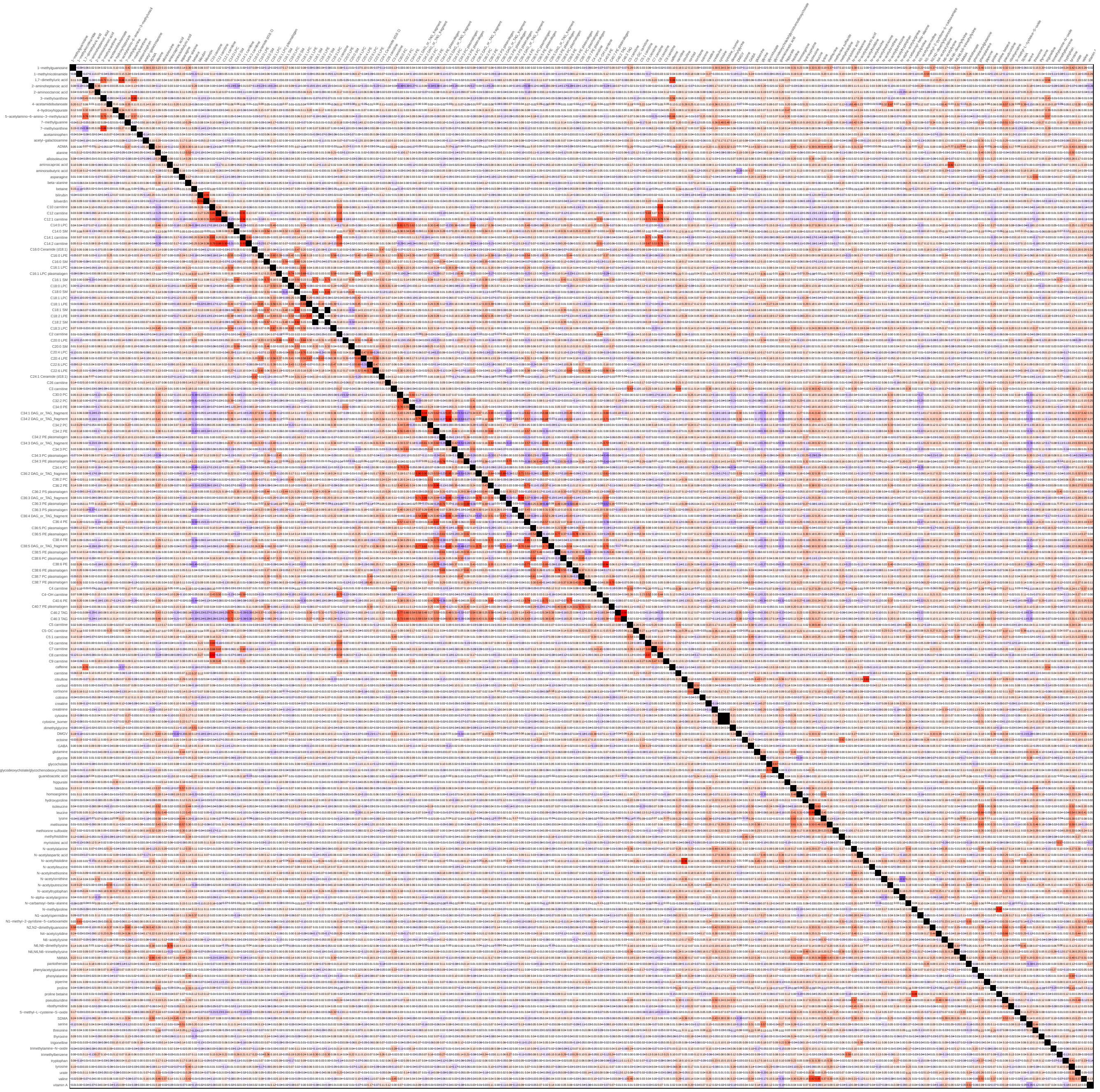
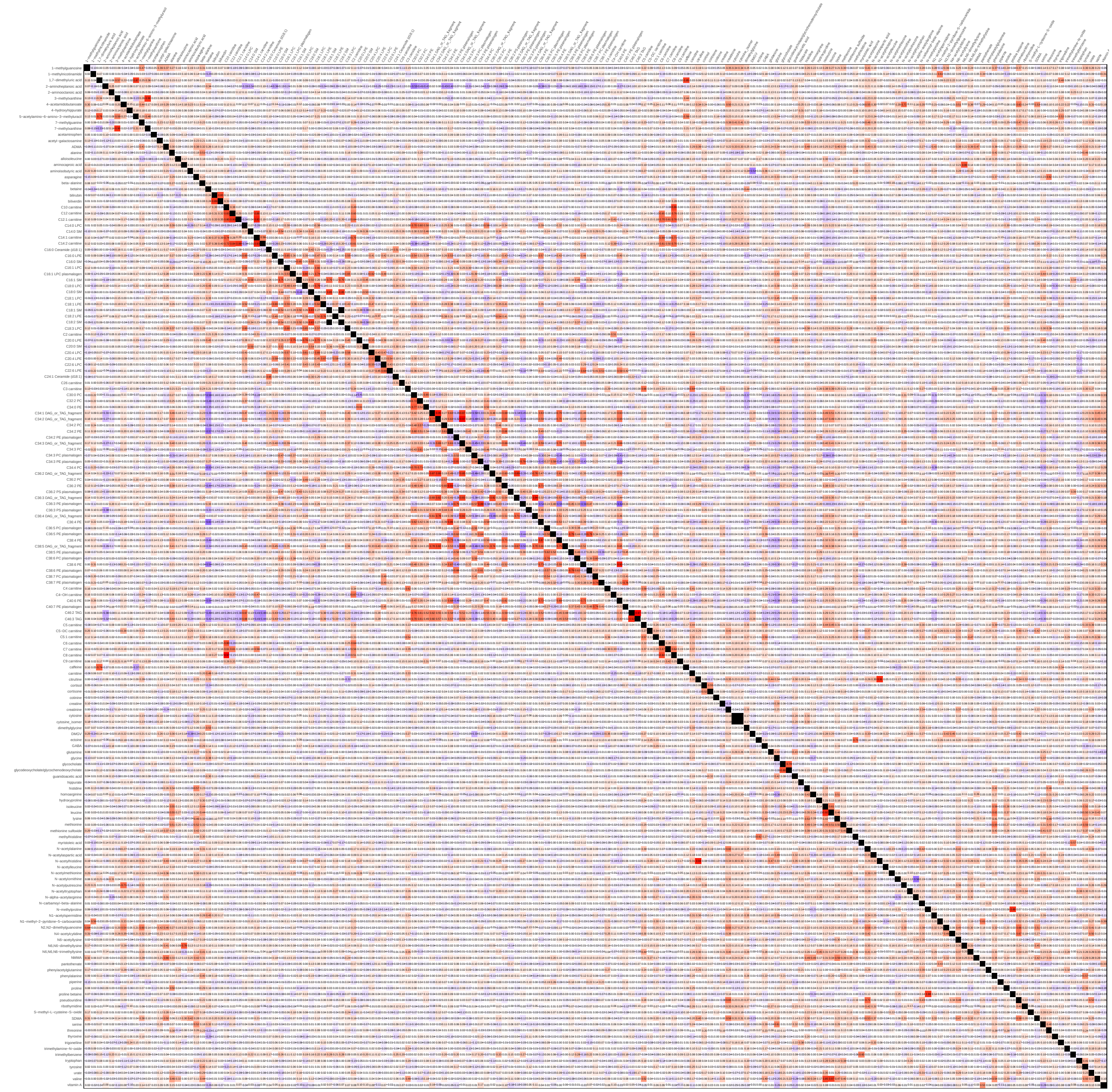
Supplemental Figure 1: Design of the type 2 diabetes case-control study with repeated metabolomics profiles. The study sample included 248 participants who remained diabetes-free for over ten years after study inception (1989/90-2000/01) and were subsequently diagnosed with type 2 diabetes (2002-2008). The 248 control were 1:1-matched for age, race/ethnicity, and blood collection date. Participants had a first metabolomics profile at study inception (1989/90) and a second after approximately ten years (2000/01), yet before diabetes incidence. Four case-control pairs had no metabolomics data at the second time point and were excluded from metabolite change analyses (244 case-control pairs with available metabolomics data at both time points).



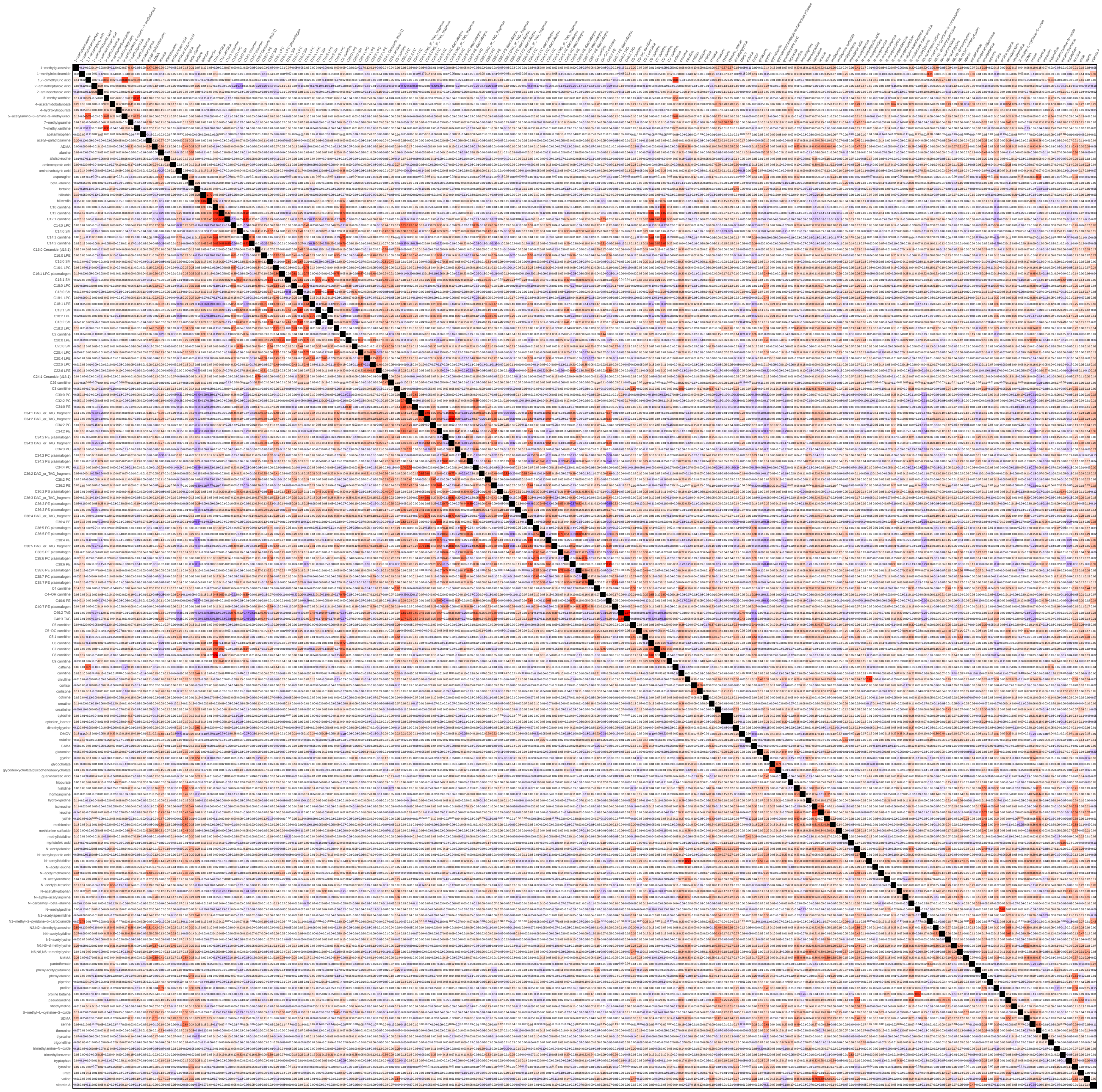
Supplemental Figure 2: Correlation and partial correlation plot across metabolites at the first blood collection (1989/90). The lower triangle shows correlation, and the upper triangle partial correlations. The numbers are Spearman correlation coefficients.



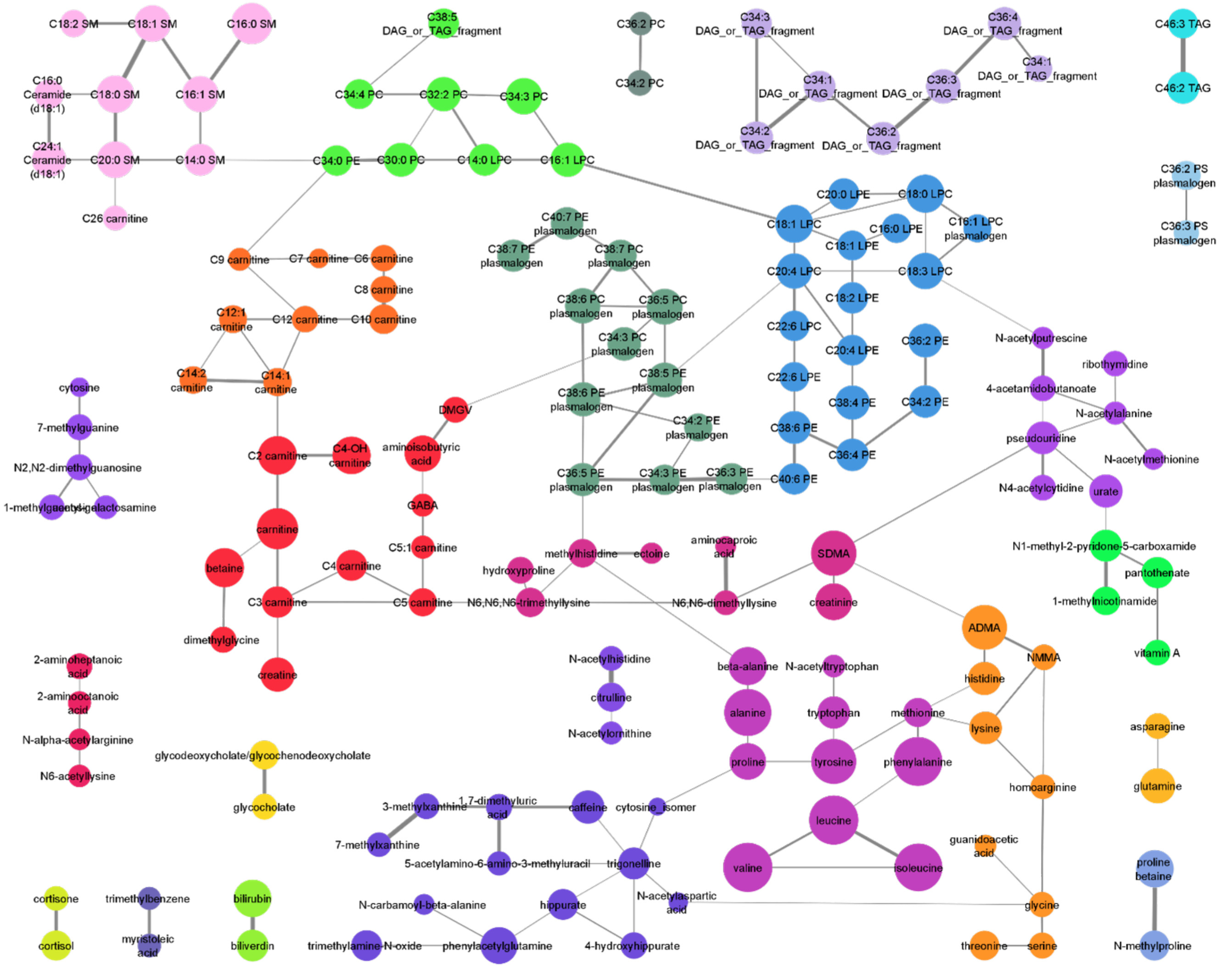
Supplemental Figure 3: Correlation and partial correlation plot across metabolites at the second blood collection (2000/01). The lower triangle shows correlation, and the upper triangle partial correlations. The numbers are Spearman correlation coefficients.



Supplemental Figure 4: Correlation and partial correlation plot across 10-year metabolite changes. The lower triangle shows correlation, and the upper triangle partial correlations. The numbers are Spearman correlation coefficients.



Supplemental Figure 5: Robust metabolomics network across 3 metabolomics profiles from two nested T2D case-control studies in the NHS cohort. Edges indicate dependencies between metabolites pairs, robust against adjustment for any subset of other metabolites, and consistently detected in network analysis of three metabolomics profiles. Among the three plasma metabolomics profiles, two were from blood specimens from the same case-control sample taken at two time points (T1: ~1990, n=496, T2: ~2001, n=488); and one was from a single baseline-blood specimen from an independent case-control sample (Sample 2, blood collection ~1990, n=960). Colors indicate clusters detected by the Louvain algorithm.



Supplemental Figure 6: Enrichment of type 2 diabetes-associated 10-year changes in human metabolic pathway-based metabolite sets. The 28% expected significant hits reflect the proportion of significant 10-year changes relative to all analyzed metabolites available in the database. Ratios indicate significant vs. available metabolites from that pathway. p-values are nominal p-values; metabolite sets with a p-value <0.1 are shown.