
Supplementary information

Microbiome and metabolome features of the cardiometabolic disease spectrum

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Supplementary Material

Microbiome and Metabolome Features of the Cardiometabolic Disease Spectrum

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Contents

Supplementary Methods

Supplementary Figure 1: Distribution of metagenomic and metabolomic features among HC, MMC and IHD groups as per the classification scheme

Supplementary Figure 2: Distribution of metagenomic and metabolomic features among HC, MMC and IHD sub-groups as per the classification scheme

Supplementary Methods

Categorization of microbiome and metabolome features across the CMD spectrum:

The deconfounded features were systematically evaluated (see **Extended Data Figure 4**) based on statistical significance, similarity of effect size, and directional alignment of microbiome and metabolome features in the various group comparisons revealing dysmetabolic-, escalation-, de-escalation- and IHD-specific features as well as subgroup-specific features (also see Figure 3 for visualization of the approach). The categorization was achieved as following:

Root: Test HC vs IHD:

1. If HC vs IHD is significant, also test HC vs MMC:

1.1. If HC vs MMC is not significant, test MMC vs IHD:

1.1.1. If MMC vs IHD is significant: IHD-specific marker.

1.1.2. If MMC vs IHD is not significant:

1.1.2.1. If both HC vs UMMC and UMMC vs IHD are significant and
HC vs

IHD is congruent with HC vs MMC: IHD-escalation marker

1.1.2.2. If both HC vs UMMC and UMMC vs IHD are significant and
HC vs IHD is incongruent with HC vs MMC: IHD de-escalation
marker

1.1.2.3. If HC vs UMMC is non-significant but UMMC vs IHD is
significant:
IHD-specific marker.

1.1.2.4. If HC vs UMMC is significant but UMMC vs IHD is
insignificant:
dysmetabolism marker.

1.1.2.5. HC vs UMMC and UMMC vs IHD are insignificant: IHD-
specific marker

1.2. If HC vs MMC is significant, test MMC vs IHD:

1.2.1. If all three are significant, and HC vs MMC is congruent with
MMC vs IHD: IHD escalation marker.

1.2.2. If all three are significant, but HC vs MMC is incongruent with MMC vs

IHD: IHD de-escalation marker.

1.2.3. If HC vs IHD, HC vs MMC are significant but not MMC vs IHD, and HC vs MMC is congruent with HC vs IHD: dysmetabolism marker

1.2.4. If HC vs IHD, HC vs MMC are significant but not MMC vs IHD, and HC vs MMC is incongruent with HC vs IHD: IHD de-escalation marker

2. If HC vs IHD is not significant but MMC vs IHD is significant, test HC vs MMC

2.1. If HC vs MMC is significant, compare directions of HC vs MMC and MMC vs IHD.

2.1.1. If HC vs MMC is congruent with MMC vs IHD: IHD escalation marker

2.1.2. If HC vs MMC is incongruent with MMC vs IHD: IHD de-escalation marker

2.2. If HC vs MMC is not significant, test HC vs UMMC and UMMC vs IHD

2.2.1. If both HC vs UMMC and UMMC vs IHD are significant and MMC vs

IHD is congruent with HC vs MMC: IHD escalation marker

2.2.2. If both HC vs UMMC and UMMC and IHD are significant and MMC vs

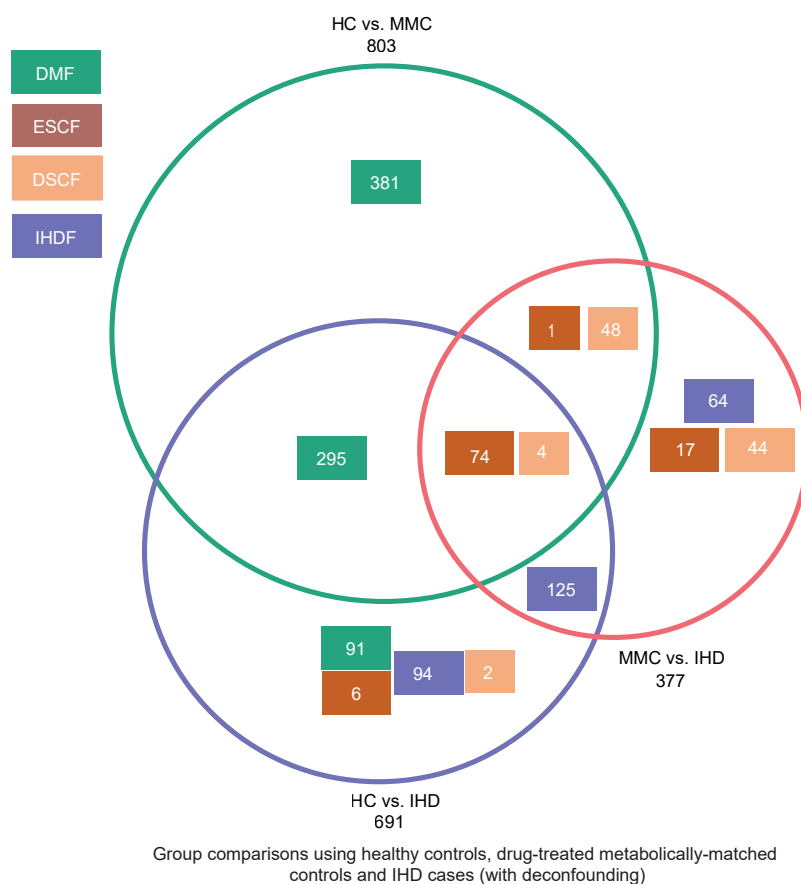
IHD is incongruent with HC vs MMC: IHD de-escalation marker

2.2.3. If HC vs UMMC is not significant but UMMC vs IHD is significant: IHDspecific marker

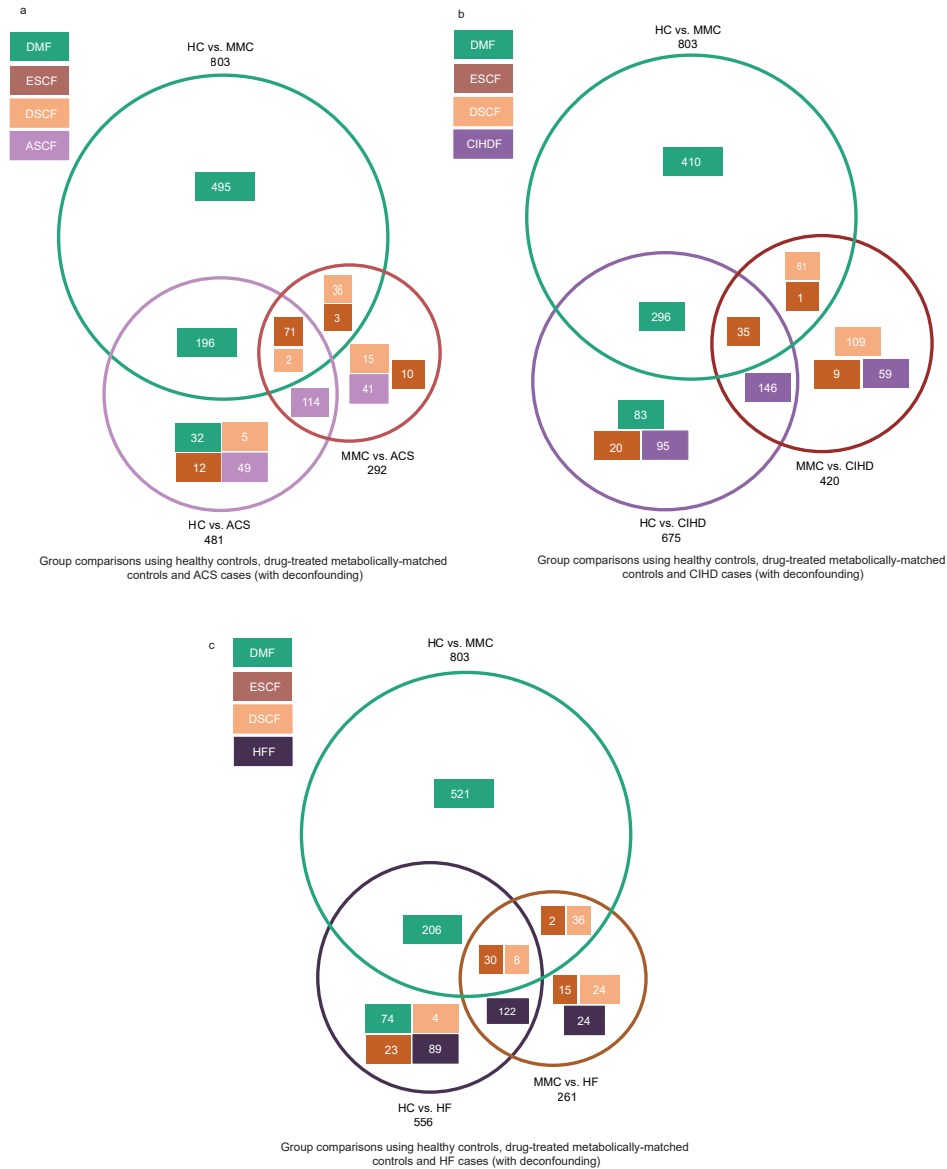
2.2.4. If HC vs UMMC is significant but UMMC vs IHD is not significant and

MMC vs IHD is congruent with HC vs MMC: IHD escalation marker

- 2.2.5. If HC vs UMMC is significant but UMMC vs IHD is not significant and MMC vs IHD is incongruent with HC vs MMC: IHD de-escalation marker.
 - 2.2.6. If both HC vs UMMC and UMMC vs IHD are insignificant: IHD-specific marker.
- 3. If HC vs IHD is NS, MMC vs IHD is NS but only HC vs MMC is significant: metabolic dysregulation marker.



Supplementary Figure 1: Distribution of metagenomic and metabolomic features among HC, MMC and IHD groups as per the classification scheme (also covered in Supplementary Table 17). Venn diagram showing the distribution of IHDF, DMF, ESCF and DSCF derived from the application of classification scheme (Extended Data Figure 4) to the HC (n = 275), drug-treated MMC (n = 372) and IHD cases (n = 372). IHD: ischemic heart disease patients, HC: healthy controls, MMC: metabolically matched controls, IHDF: IHD specific features, ESCF: escalation features, DSCF: De-escalation features, DMF: dysmetabolism features.



Supplementary Figure 2: Distribution of metagenomic and metabolomic features among HC, MMC and IHD sub-groups as per the classification scheme (also covered in Supplementary Table 17). Venn diagram showing the distribution of subgroup specific, ESCF, DSCF and DMF when classification scheme (Extended Data Figure 4) was applied to ACS (n = 112), CIHD (n = 158) and HF (n = 102) groups relative to drug-treated MMC (n = 372) and HC (n = 275). HC: healthy controls, MMC: metabolically matched controls, ACS: acute coronary syndrome, CIHD: chronic IHD, HF: heart failure due to CIHD, ACSF: ACS specific features, CIHDF: CIHD specific features, HF specific features, ESCF: escalation features, DSCF: De-escalation features, DMF: dysmetabolism features.