RESEARCH ARTICLE

Degraded ecosystem soil and type 2 diabetes gut microbiomes share altered potential metabolism for sugars, lignin and branched-chain fatty acids: a blind spot for global health?

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Abstract

The global rise in human allergic and autoimmune diseases is linked to altered environmental microbiome exposures from increasing land use change, ecosystem degradation and biodiversity loss. Yet, microbiome-mediated impacts of global change on metabolic health have received little attention. Type 2 diabetes (T2D) is a complex metabolic disease with rapidly increasing global prevalence, uncertain pathogenesis and influences from gut microbiome-host interactions and environmental factors. Soil microbiomes shift in composition and functional capacity with ecosystem condition and are an important source for priming and resupplying the human gut microbiome, which is critical in metabolism. Here, we sought to examine overlapping functional capacities in model case study microbiome datasets from (1) soils from a gradient of ecosystem quality (from highly disturbed to mature/natural sites under forest ecosystem restoration) and (2) gut microbiomes in T2D versus normal health to investigate plausible links between ecosystem degradation and metabolic anomalies encoded in T2D gut microbiomes. We developed a novel method to translate microbiome functional capacities (i.e., functional gene-associated biochemical pathway relative abundances) to 'compound processing potential' (CPP, %), reflecting the potential metabolism of individual compounds. Examining selected compounds relevant to soil and gut health, and via exhaustive compound-wide trend analyses, we identified compounds that shared potential metabolism trends. We found increased potential metabolism for sugars and decreased potential metabolism for lignin and monomethyl branched-chain fatty acids, in both T2D and degraded ecosystems. These trends were confirmed in two separate T2D case study cohorts from Sweden and China, suggesting a generalizable pattern. Our findings support a consequential new hypothesis that excessive exposures to degraded ecosystem soil microbiomes may distort gut microbiome functional capacities and metabolism and thereby contribute to type 2 diabetes.

1. Introduction

Environment and lifestyle exposures under the global trends of land use change, ecosystem degradation, biodiversity loss, urbanization and reduced nature contact are associated with many non-communicable diseases, including several with suspected microbiome-mediated links (Flandroy et al., 2018; Flies et al., 2019; Roslund et al., 2022). Among these, type 2 diabetes (T2D) is a major chronic multifaceted metabolic disease with uncertain pathogenesis, characterized by insulin resistance, loss of insulin secretion, high blood sugar levels and wider metabolic dysregulation (Beulens et al., 2022; Lu et al., 2024; Pearson, 2019). Growing evidence supports the influence of gut microbiomes on human metabolic health and dysfunction. However, there is a pressing need to better understand the contribution of microbiomes in T2D (Cunningham et al., 2021; Gurung et al., 2020) due to their potential mediating influence via diet, lifestyle and environmental factors. The role of environmental microbiomes in supporting human metabolic health remains understudied (Flandroy et al., 2018)—particularly in the context of accelerating global change (IPBES, 2018). T2D is a major contributor to the global non-communicable disease pandemic (Cheema et al., 2014) and represents ~96% of total diabetes cases, which impacted 529 million people in 2021 (6.1% prevalence; costing US$966 billion), and is expected to rise to 1.31 billion people by 2045-2050 (10% prevalence; costing US$1.05 trillion) (Ong et al., 2023; Sun et al., 2022).

The human gut microbiome is directly involved in our metabolism, shaping the biochemical profile of our diet via an extensive metabolic repertoire that is distinct yet complementary to mammalian digestive enzymes (Rowland et al., 2018). The gut microbiome and its diet-derived metabolites influence human physiology and energy regulation by modulating appetite, energy harvest, gene expression, gut motility, and the conversion and storage of dietary energy (Chao et al., 2025; Krajmalnik-Brown et al., 2012). Specifically, in T2D shifts in gut microbiome community and functional composition have been compared to normal healthy subjects, which are in part alleviated by

75 treatment with the antidiabetic drug metformin (Forslund et al., 2015). Moreover, fecal microbiome
76 transplantation studies have demonstrated amelioration of clinical indicators of T2D (Chen et al., 2023;
77 Wu et al., 2023). Long-term diet is a key factor shaping gut microbiome composition (Gilbert et al.,
78 2018), and diet shaped by the gut microbiome can modify the expression and operation of intestinal
79 enteroendocrine cells (EECs) responsible for sensing and responding to nutrients (e.g., shifting from
80 serotonin to peptide producing EECs, or microbiome-dependent silencing of EECs; Aliluev et al.,
81 2021; Ye et al., 2019). These are multidirectional interactions, as loss of EECs and their secreted
82 hormones also changes microbiome structures (Blot et al., 2023).

83 Intriguingly, numerous assessments attribute a major share of T2D risk to environmental
84 exposures that extend well beyond lifestyle and dietary behaviors to include the built, natural, social,
85 and physicochemical environments (Beulens et al., 2022). Among these, strong population-level
86 evidence links T2D to a shift in living environments from rural to rapidly growing, densely populated
87 urban areas (Attard et al., 2012; Cheema et al., 2014; Gassasse et al., 2017; Ruiz-Alejos et al., 2018).
88 Importantly, microbiomes represent a key potential linkage mechanism between environmental
89 exposures consistent with T2D risk and metabolic processes occurring in the human gut. Gut
90 microbiomes are predominantly shaped by environmental factors, including diet and ambient
91 exposures, not host genetics (Rothschild et al., 2018). In particular, soils represent a rich source of
92 environmental microbial exposures, providing home to 59% to >99.9% of species on Earth (Anthony et
93 al., 2023; Blakemore, 2025). The gut is dominated by spore-forming bacteria, together with facultative
94 anaerobes, capable of surviving and dispersing through aerobic environments before re-establishing in
95 suitable oxygen-deprived habitats (e.g., lower intestine, wet organic-containing soil habitats) (Browne
96 et al., 2016; Wyres & Holt, 2018). Exposure to naturally biodiverse soil microbiomes shapes and
97 supplements gut microbiome composition and functional capacity, particularly from a young age
98 (Liddicoat et al., 2020; Liu et al., 2021; Roslund et al., 2021; Zhou et al., 2024). Consequently, soil

99 microbes may be introduced to the gut environment through direct soil contact, foodborne and airborne
100 (e.g., dust) microbiomes. Moreover, soil microbiome composition and functional capacity may shift in
101 generalizable ways with ecosystem quality (i.e., spanning anthropogenically disturbed/degraded to
102 intact natural condition), with potential to impact human health (Delgado-Baquerizo et al., 2021;
103 Liddicoat et al., 2024; Liddicoat et al., 2022). As urbanization accelerates—with around 70% of the
104 global population projected to live in cities by 2050 (UNDESA, 2019)—the degradation and
105 homogenization of soil microbiomes in urban and peri-urban environments may pose growing risks to
106 human health (Sun et al., 2023). Exploring overlaps in the functional capacities of (1) naturally
107 biodiverse versus degraded soil microbiomes (linked to aboveground degraded versus intact ecosystem
108 condition) and (2) normal healthy versus T2D gut microbiomes, may reveal previously unappreciated
109 microbiome linkages between environments and T2D.

110 Despite their importance, the measurement and definition of 'healthy microbiomes' in humans
111 and soils remain challenging (Fierer et al., 2021; Van Hul et al., 2024). Approaches that examine the
112 range of functions performed by microbiomes are expected to offer improved understanding compared
113 to measures based on compositional diversity (Van Hul et al., 2024). Community-scale microbial
114 metabolism, where bioenergetic machinery and resources (including metabolites and electron transfer)
115 are shared in the extracellular space (Daisley et al., 2021), adds complexity and means that multiple
116 taxa may often combine to perform functional roles of interest. The need for improved insight into the
117 contributions of microbiomes in health and disease has motivated efforts to analyze soil and gut
118 microbiomes through the lens of their *compound processing potential* (CPP) (Liddicoat et al., 2024;
119 Figure S1). A compound-oriented approach can provide more direct functional information about
120 microbiomes because of known biochemical and health associations with chemical compounds (e.g.,
121 microbial feedstocks, substrates and metabolites, such as carbohydrates, lipids, proteins, amino-sugars,
122 vitamins), which are not described for most microbial taxa. New insights into differential compound

processing by microbiomes may also point to mechanistic hypotheses and/or possible therapeutic targets. Microbial metagenomes (the entire collective DNA of a sample) are used to examine functions. However, existing approaches require specialized knowledge of complex biochemical pathways and do not provide resolution at the fundamental level of the chemical compounds involved (i.e., individual compounds may often participate in multiple pathways). Existing metabolite prediction frameworks are also unsuited to highly biodiverse and varying environments, such as soils (Liddicoat et al., 2024). Thus, there is a need for new, compound-oriented methods to examine healthy functioning in soil and gut microbiomes.

Here we explore and compare model case study soil and gut metagenome datasets from a gradient of ecosystem quality and in subjects with T2D versus normal health by quantifying their genomic potential to metabolize an array of chemical compounds. Specifically, the aims were to improve functional and metabolic insights to the role of microbiomes in ecosystems and T2D, and their potential overlaps, through identifying: (1) compounds with differential potential metabolism (i.e., with trending CPP) based on analysis of soil metagenomes across an ecosystem quality gradient (i.e., degraded to intact natural condition); (2) compounds with differential potential metabolism (based on CPP values) from gut metagenomes in health versus untreated T2D; and (3) overlapping compounds and biochemical/functional pathways between (1) and (2) that may reveal new insights to potential environmental microbiome contributions to T2D.

2. Materials and Methods

2.1. Case study data

We examined three model case study datasets (Table 1) comprising previously published (1) soil metagenomes from a restoration gradient case study that compared degraded post-mining, reforested, and unmined reference sites (Sun & Badgley, 2019), and (2) gut metagenomes from subjects with

147 untreated T2D and normal healthy controls (Forslund et al., 2015). We determined CPP trends with
148 restoration (described below), however, our subsequent focus is to characterize potential metabolism
149 outcomes associated with degraded ecosystems that correspond to the more disturbed soil microbiomes
150 in the younger revegetation age samples of the restoration gradient. We used two T2D datasets
151 comprising separate case study cohorts. The first T2D dataset from Sweden (Karlsson et al., 2013) was
152 analyzed to identify differences in CPP or potential metabolism in T2D, and then assess overlaps with
153 trending CPP found in more degraded (towards younger) samples from the restoration gradient case
154 study. A second T2D dataset from China (Qin et al., 2012) was then integrated to confirm and
155 consolidate trends in compound-level potential metabolism that emerged consistently across all three
156 case studies.
157
158 **Table 1.** Description of case study metagenome datasets.

Case study	**Main comparison groups (and sample/subject numbers)**	**Metagenome functional profile characteristics (sample mean ± s.d.)**	**Source data reference; sequencing platform**	**Study nation of origin**
Soil				
Post-mining forest ecosystem restoration ('restoration gradient')	Soil samples spanned revegetation ages of 6, 12, 22, 31 years, and unmined (UM) samples (treated as ordinal variables). Comprising five age-based groups, each with three replicates. Total *n* = 15	Functions (SUPER-FOCUS): *n* = 30,125 (20,328 ± 767). Functional % all sum to 100%. Compounds (CPP profiling): *n* = 8,370 (7,777 ± 92). CPP (%): (67 ± 0.4 %)	MG-RAST project mgp16379 (Sun & Badgley, 2019); Illumina HiSeq	United States
Human gut				
Type 2 diabetes	T2D with no metformin treatment (T2D met-, *n* = 33),	Functions (SUPER-FOCUS): *n* = 17,962 (7861 ± 1699).	SRA accession PRJEB1786	Sweden

(T2D) vs. Normal	vs. normal healthy (*n* = 43). Subjects were females only, aged 69-72 years. Total *n* = 76	Functional % all sum to 100%. Compounds (CPP profiling): *n* = 7,031 (5,292 ± 584). CPP (%): (70.5 ± 2.9 %)	(Forslund et al., 2015; Karlsson et al., 2013)[a]; Illumina HiSeq	
T2D vs. Normal (Validation dataset)	T2D met- (n = 30; females *n* = 17, aged 51-71 years; males *n* = 13, aged 51-75 years). Normal (*n* = 52; females *n* = 24, aged 51-67 years; males *n* = 28, aged 52-74 years). Total *n* = 82	Functions (SUPER-FOCUS): *n* = 19,363 (8677 ± 4212). Functional % all sum to 100%. Compounds (CPP profiling): *n* = 7,206 (5,329 ± 1644). CPP (%): (65.7 ± 4.1 %)	SRA accession PRJNA422434 (Forslund et al., 2015; Qin et al., 2012)[a]; Illumina Genome Analyzer II	China

Note: [a]Forslund et al. (2015) applied metformin treatment data in a reanalysis of metagenome data from Swedish (Karlsson et al., 2013) and Chinese (Qin et al., 2012) cohorts. We analyzed a subset of each cohort. From the Swedish cohort, we excluded subjects who were treated with metformin or diagnosed with impaired glucose tolerance (prediabetes). From the Chinese cohort, used here for validation purposes, we only included subjects >50 years old to compare with the mature age (69-72 years) Swedish subjects.

2.2. Metagenome functional profiling via compound processing potential (CPP)

The CPP analysis approach uses a novel bioinformatics workflow that redistributes values of conventionally derived functional potential relative abundances (%), from the scale of functions (i.e., biochemical pathways that often comprise multiple linked chemical reactions), down to the level of the individual chemical compounds. These compounds are conceptually participating in the array of intersecting chemical reactions represented in the collective functional capacity of a metagenome. These methods do not measure actual chemical compounds. Rather, they quantify the genetic capacity of a microbial community to metabolize (or process) compounds, as written in the metagenome. The distinction is not made between compounds being consumed (reactants) or produced (products) as

175 functional pathways may often involve strings of chemical reactions (metabolic processes), involving
176 one or many organisms, where a compound can be the output of one reaction and an input to another.
177 Measures of CPP were derived following the steps outlined in Figure 1. Firstly, following
178 Liddicoat et al. (2024), raw metagenomic sequences were accessed, trimmed for quality control, then
179 classified to SEED subsystem (Overbeek et al., 2013) functional annotations and relative abundances
180 using SUPER-FOCUS software (Silva et al., 2015). Every SUPER-FOCUS function (output row) was
181 translated to one or more corresponding chemical reaction(s) using a purpose-built R-script algorithm
182 based on ModelSEED database lookup tables (from
183 https://github.com/ModelSEED/ModelSEEDDatabase; accessed 10 Aug 2022). Linking of functions to
184 chemical reactions was based on either: full matching of functional hierarchies (using subsystem-class,
185 -subclass, -name and -role); detection of Enzyme Commission (EC) number; or matching of SUPER-
186 FOCUS function name within ModelSEED lookup tables for reactions (reaction name or alias),
187 subsystems (role), or reaction-pathways (external reaction name). Reactions were then linked to
188 corresponding compounds using ModelSEED database tables ('reactions.tsv', 'compounds.tsv').
189 Advancing from the previous method used in Liddicoat et al. (2024), we derived CPP measures at the
190 resolution of individual compounds (all software parameters and supporting R code for CPP
191 calculations are available at: https://github.com/liddic/cpp3d_t2d):
192 a. Function level relative abundances from SUPER-FOCUS (which sum to 100% in each sample)
193 were allocated to compounds by dividing values equally across all sub-functions and reactions,
194 and dividing again across all corresponding compounds, with weightings to account for
195 stoichiometric coefficients for each compound within each reaction, with equal consideration to
196 reactant and product compounds.
197 b. Relative abundances (%) for respective unique compounds (which may arise across multiple
198 reactions and functions/pathways) were then collated and summed to provide a summary CPP

relative abundance (%) for each compound. (Here, conversion to CPP data format successfully recovered typically 65 to 70% of the initial 100% function potential per sample; Table 1).

c. To assist further mapping visualization of CPP patterns for carbon-containing compounds, elemental ratios of O:C, H:C, and N:C were calculated. Such chemical mapping frameworks have been used previously to display and interpret groupings of energetically and chemically similar compounds (Liddicoat et al., 2024; Rivas-Ubach et al., 2018).

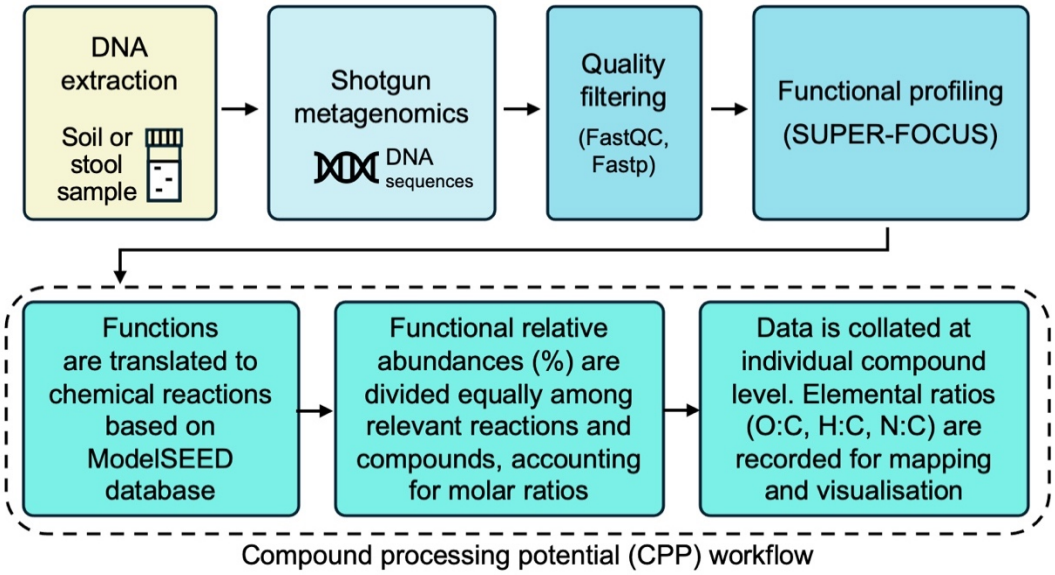

Figure 1. Overview of the CPP analysis workflow used to translate microbial metagenome functional potential relative abundances to quantify potential metabolism at the level of individual compounds.

2.3. Statistical Analysis

We used a staged approach to explore overlapping potential metabolism (i.e., CPP) trends in the restoration gradient (soil) and T2D gut samples (further detail is in Supplementary Material and at https://github.com/liddic/cpp3d_t2d):

a. ***Thirty selected compounds*** were chosen due to their relevance to soil and/or gut health (e.g., Blanco-Pérez et al., 2021; Daisley et al., 2021; Krajmalnik-Brown et al., 2012; Six et al., 2006;

compounds and reference information are listed in Table S1). For this list of compounds, CPP trends were evaluated using Kendall's tau rank correlation tests based on ordinal revegetation age classes. We interpreted CPP trends with ecosystem degradation as the inverse of calculated trends with increasing revegetation age (towards intact natural condition). This assumption that degradation may be modelled as the opposite of restoration is based on previous work showing highly disturbed post-mining soil microbiomes progressively shift in their structure with ecosystem restoration (Liddicoat et al., 2022). CPP trends (i.e., differences) with T2D versus normal health were evaluated using non-parametric Wilcoxon rank-sum (Mann-Whitney) tests, due to often differing variance of groups (T2D vs. normal) and to avoid normality assumptions. All data were plotted to assist interpretation.

b. ***Compound-wide association tests*** were also performed to exhaustively scan all compounds represented in the respective CPP datasets, using the same trend evaluation methods as above. In soils, compounds that did not have relative abundance data for at least a quarter of the total sample number were excluded due to low data. In soils, strong trends were discovered, and only significant results based on adjusted *P*-values were considered further (i.e., after applying Benjamini and Hochberg false discovery rate correction). In the separate compound-wide analysis of T2D gut samples, compounds were only included if at least one or other of the T2D or normal groups contained at least 50% non-zero CPP values. Testing was based on $\log_{10}$-transformed CPP % values, after zero replacement with small positive values equal to half the minimum non-zero CPP % of all samples. One-sided (directional) difference tests were based on whether the median value in T2D was greater or less than the median value for normal healthy subjects. The T2D (Swedish cohort, SWE) Wilcoxon rank sum test results yielded many *P*-values < 0.05. However, none were low enough to withstand Benjamini and Hochberg *P*-adjustment for multiple testing, therefore, *P*-adjustment was not performed in the compound-

240 wide T2D gut data to retain the most interesting (potentially significant) results for further
241 exploration.

242 c. ***Overlap analysis.*** Compounds with CPP % trends in both the restoration gradient and T2D
243 (SWE) case studies were identified, based on matching ModelSEED compound identifiers. Our
244 focus was to highlight compounds that displayed consistent increases or decreases in CPP %
245 with degraded/disturbed ecosystems (i.e., towards younger revegetation age) and in T2D.

246 d. ***Visualising compound-wide association test results.*** Next, compounds with CPP % trends in
247 the restoration gradient and T2D (SWE) gut microbiomes, and overlaps between the two, were
248 mapped using their chemical formula elemental ratios of O:C, H:C, and N:C. From this
249 mapping space, prominent localized clusters of consistently trending compounds (i.e., with
250 ecosystem degradation and T2D) were identified and further analyzed to determine trends in
251 their collective (summed) CPP % and to interpret their possible metabolic importance.

252 e. ***Trend confirmation and consolidation.*** The above steps were repeated with the second T2D
253 (Chinese cohort, CHN) dataset, which ultimately refined the list of individual compounds with
254 parallel trends in CPP % across all datasets. Trend and contextual information for these
255 compounds was reported and visualised to represent the significance ($-\log_{10}(P\text{-value})$; as used in
256 genome-wide association study Manhattan plots) of their association with disturbed/degraded
257 ecosystems and T2D, and the number of functional themes (level 3 subsystems) they are linked
258 to. Here, data for T2D were visualised using mean results from the Swedish and Chinese cohort
259 datasets.

260 f. ***Beta diversity ordinations.*** Supplementary analyses were performed to examine community-
261 scale compositional patterns and differences between sample groups and analysis approaches,
262 comparing conventional functional potential (%) data (termed 'functions') versus CPP (%) data.
263 This analysis used principal coordinate analysis (PCoA) ordinations based on Bray-Curtis

distances, and testing for differences between groups via permutational analysis of variance (PERMANOVA) and beta dispersion testing for homogeneity of groupings using the vegan R package (Oksanen et al., 2020). These data are presented in the Supplementary Material, Supporting Information and Figure S2.

3. Results

3.1. Potential metabolism trends with ecosystem degradation

Analysis of CPP trends for 30 selected compounds (Table S1; Figures S3-S32) found increased potential metabolism with ecosystem degradation for (very strong evidence, $P < 0.001$) fructose (Kendall's tau ~restoration, $\tau = -0.761$), sucrose ($\tau = -0.782$), arabinose ($\tau = -0.844$), glucose ($\tau = -0.802$), xylose ($\tau = -0.761$) and chitin ($\tau = -0.782$); also (strong evidence, $P < 0.01$) galactose ($\tau = -0.617$), mannose ($\tau = -0.597$) and hydrogen sulfide ($\tau = -0.617$); and (moderate evidence, $P \leq 0.05$) glucosamine ($\tau = -0.514$) and arabinoxylan (hemicellulose) ($\tau = -0.453$). Conversely, we found decreased potential metabolism with ecosystem degradation for ($P < 0.001$) acetate ($\tau = 0.72$), carbon dioxide ($\tau = 0.844$) and lignin ($\tau = 0.802$); also ($P < 0.01$) glycogen ($\tau = 0.597$), butyrate ($\tau = 0.658$), trimethylamine N-oxide ($\tau = 0.576$) and trimethylamine ($\tau = 0.555$); and ($P \leq 0.05$) propionate ($\tau = 0.432$) and methane ($\tau = 0.473$).

Compound-wide ordinal correlation trend analyses identified 2,122 compounds with significant trends ($n = 757$ increasing, $n = 1{,}365$ decreasing with revegetation age; compound and trend data are in Supplementary Material files). Carbon-containing compounds were mapped using chemical formula ratios O:C, H:C and N:C (Figure 2; $n = 720$ increasing, $n = 1{,}255$ decreasing with revegetation age) to visualize clusters of compounds of similar chemical and energetic composition that trend together. We interpreted trends with ecosystem degradation as the opposite of the visualized trends with revegetation

age (restoration). An example plot visualizing all carbon-containing compounds within a single sample is provided in Figure S33.

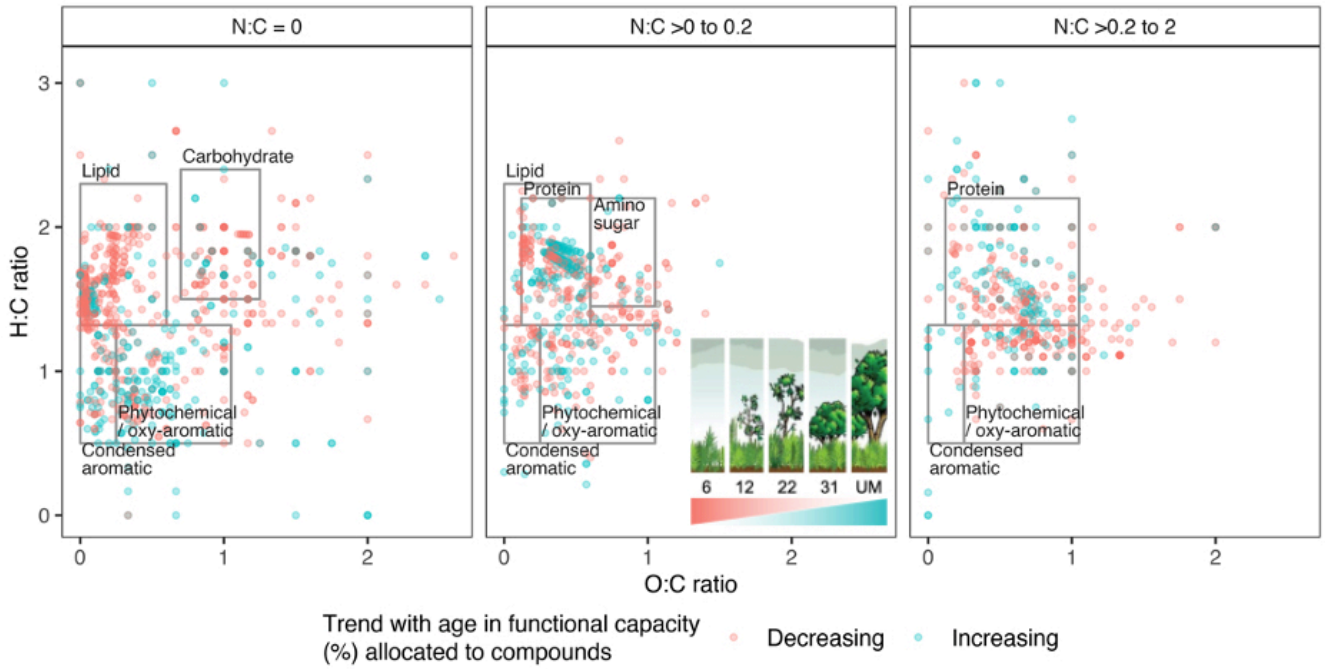

Figure 2. Compound-wide trend analysis results derived from soil metagenomes (described in Table 1), showing carbon-containing compounds with increasing (aqua, *n* = 720) or decreasing (red, *n* = 1,255) compound processing potential (CPP, i.e., functional capacity % or potential metabolism at individual compound scale) with revegetation age. Each point represents a compound, mapped via its chemical formula O:C, H:C and N:C elemental ratios. Only compounds that have trending potential metabolism (i.e., shifting CPP % values) from degraded to mature/natural ecosystem quality are displayed. Clusters of points indicate energetically and chemically similar compounds. The O:C by H:C panels are zoomed in from their full extent to improve visualization of more data-rich regions. N:C ratios are displayed as three depth-slices to represent the third dimension. Rectangular zones denoting compound classes are provided as a visual guide only (adapted from Rivas-Ubach et al., 2018; Wu et al., 2018).

302

303 **3.2. Potential metabolism trends in T2D**

304 In the 30 selected compounds, we found consistent trends in the Swedish (SWE) and Chinese (CHN)
305 cohort datasets (Table S1; Figures S3-S32, S34) for increased potential metabolism in T2D for fructose
306 (SWE: $P \leq 0.05$, CHN: $P < 0.001$), arabinose (SWE: $P \leq 0.05$, CHN: $P < 0.001$), and amylopectin and
307 amylose (SWE and CHN: $P \leq 0.05$). We found decreased potential metabolism in T2D for lignin (SWE
308 and CHN: $P \leq 0.05$).

309 Numerous trends were only found in one T2D cohort or the other. Increased potential
310 metabolism was found in T2D in the Swedish cohort for sucrose and starch ($P \leq 0.05$), and in the
311 Chinese cohort for mannose ($P < 0.001$); glucose, galactose and xylose (all $P < 0.01$). Decreased
312 potential metabolism was found in T2D in the Chinese cohort for acetate, propionate, butyrate, carbon
313 dioxide, hydrogen sulfide, Menaquinone (Vitamin K2), indole (all $P < 0.001$); glucosamine ($P < 0.01$);
314 methane, p-cresol and serotonin (all $P \leq 0.05$). We found conflicting potential metabolism trends for
315 ammonia across the cohorts, which increased in Swedish ($P < 0.01$) but decreased in Chinese ($P <$
316 0.001).

317 The compound-wide Wilcoxon rank sum trend analyses in T2D Swedish and Chinese cohorts
318 identified similar numbers of compounds with increased potential metabolism, but substantially higher
319 numbers of compounds with decreased potential metabolism in the Chinese cohort (visualized in
320 Figures S35 and S36; compounds and trend data for both T2D datasets are available in Supplementary
321 Material). For consistency, across both compound-wide T2D association analyses, and to retain the
322 most interesting T2D (SWE) cohort data, these data were not subject to *P*-adjustment for multiple
323 testing. In the T2D (SWE) data, a total of 1243 compounds with trending potential metabolism (n =
324 915 decreased, $n = 328$ increased) were found. From these, a total of 1158 carbon-containing
325 compounds ($n = 864$ decreased, $n = 294$ increased) were mapped using chemical formula ratios O:C,

326 H:C and N:C (Figure S35). For the T2D (CHN) data a total of 4299 compounds (*n* = 3965 decreased, *n*
327 = 334 increased) were identified, corresponding to 3970 carbon-containing compounds (*n* = 3678
328 decreased, *n* = 292 increased) mapped using chemical formula ratios O:C, H:C and N:C (Figure S36).
329 From visual inspection (comparing Figures S35 and S36), the chemical ratio mapping displays some
330 zones of similarity (e.g., in the vicinity of carbohydrates) but also dramatic differences due to the
331 widespread number of compounds with reduced potential metabolism in the T2D (CHN) dataset.
332

333 **3.3. Consistent CPP trends with ecosystem degradation and T2D**

334 Within the list of 30 selected compounds (Table S1), we found limited cases of consistent potential
335 metabolism trends across all three datasets – i.e. with ecosystem degradation, T2D (SWE), and T2D
336 (CHN). Specifically, we found increased potential metabolism in fructose and arabinose and decreased
337 potential metabolism in lignin was consistent across all datasets (Table S1).

338 Using the compound-wide trend results from T2D (SWE) and restoration gradient datasets, we
339 performed an overlap analysis, based on matching ModelSEED compound identifiers, to highlight
340 compounds with potential metabolism trends across both case study scenarios (compound and trend
341 data are in the Supplementary Material). From a total of 276 compounds that had CPP trends with T2D
342 (SWE) and across the restoration gradient, 260 carbon-containing compounds were visualized through
343 chemical ratio mapping (Figure 3). Decreased CPP (i.e., potential metabolism) with T2D (SWE) and
344 ecosystem degradation was observed in 70 compounds (66 contained carbon; red dots in Figure 3).
345 Increased CPP with T2D (SWE) and ecosystem degradation was observed in 58 compounds (52 with
346 carbon; green dots in Figure 3). Matching trends with ecosystem restoration were also found.
347 Decreased CPP with T2D (SWE) and ecosystem restoration was observed in 98 compounds (93
348 contained carbon; yellow dots in Figure 3). Increased CPP with T2D (SWE) and ecosystem restoration
349 was observed in 50 compounds (49 with carbon; blue dots in Figure 3).

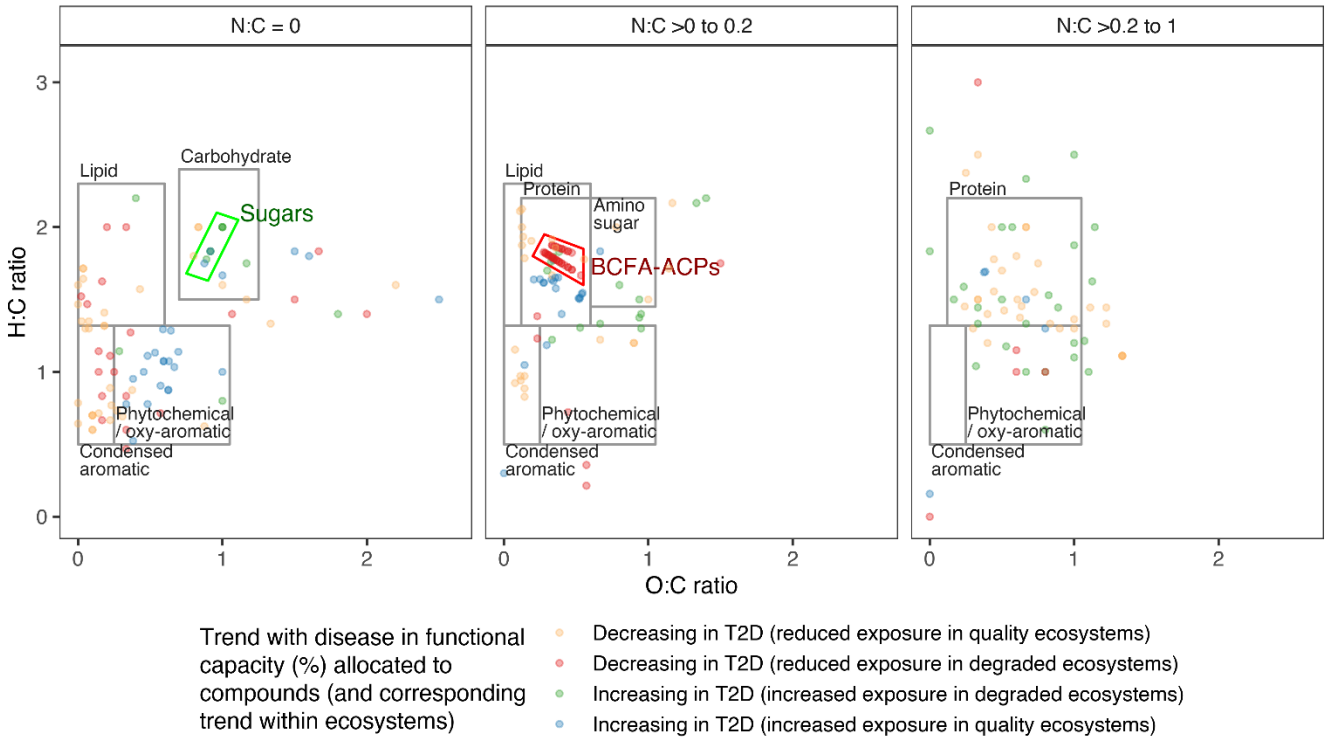

Figure 3. Overlap analysis showing carbon-containing compounds with trending potential metabolism in both compound-wide trend analyses of the T2D (Swedish cohort) and restoration gradient case study datasets (i.e., this plot shows overlapping compounds from Figures 2 and S35). Clusters of each color represent energetically and chemically similar compounds occurring in each of the four trend groups listed (numbers of compounds are provided in the text). Further description of the plot format is provided in Figure 2. Expanded views of the grouped 'sugars' and branched-chain fatty acid - acyl-carrier proteins (BCFA-ACPs) are provided in Figures S37-S41.

360 With our focus on microbiome functional shifts with ecosystem degradation, and to further
361 explore compounds that also shared potential metabolism trends with T2D (SWE), we inspected the
362 mapping visualization in Figure 3 and observed two prominent clusters of compounds with matching
363 trends (also see Table S2-S3, Figures S37 and S39). The first group outlined in green and labelled
364 'Sugars' in Figure 3 comprised six carbohydrate compounds (L-arabinose, melibiose, manninotriose,
365 D-lyxulose, sucrose, D-fructose; Table S2) that all display increasing CPP in both T2D (SWE) and
366 with ecosystem degradation. In the O:C, H:C, N:C mapping space, these sugars all occur on the line
367 H:C = 2 × O:C, with N:C = 0 (i.e., green points in Figure S37). Analysis of summed CPP values for
368 these sugars showed that they collectively exhibit a very strong increase with ecosystem degradation
369 (Kendall's tau ~restoration = -0.844, P = <0.001) and a strong increase in T2D (SWE) (Wilcoxon rank
370 sum W = 984, P = 0.002) (Figures 4 and S38).
371 The second group outlined in red in Figure 3 comprised 35 unique compounds involved in fatty
372 acid biosynthesis. This group was labelled BCFA-ACPs (branched-chain fatty acid – acyl-carrier
373 proteins) as it is dominated by this type of compound (n = 30), together with n = 5 straight-chain fatty
374 acid-ACPs (Table S3). All compounds in the BCFA-ACPs group have reduced CPP in T2D (SWE) and
375 reduced CPP in disturbed ecosystems, and they each occur on two straight lines in the O:C, H:C, N:C
376 mapping space (line 1: H:C = -0.625 × O:C + 2, and line 2: H:C = -0.375 × O:C + 2, where N:C is in
377 the range >0 to 0.2; Figure S39). Analysis of summed CPP values for the BCFA-ACPs group showed
378 that they collectively exhibited a very strong decrease with ecosystem degradation (Kendall's tau
379 ~restoration = 0.741, P = <0.001) and also moderate reduction in T2D (SWE) (Wilcoxon rank sum W
380 = 513, P = 0.02) (Figures 4 and S40). When the summed CPP data for these groups were validated in
381 the T2D Chinese cohort data, they showed very strong agreement (sugars: Wilcoxon rank sum W =
382 1146, P <0.001, BCFA-ACPs: W = 336, P <0.001; Figure 4, detailed plot in Figure S41).

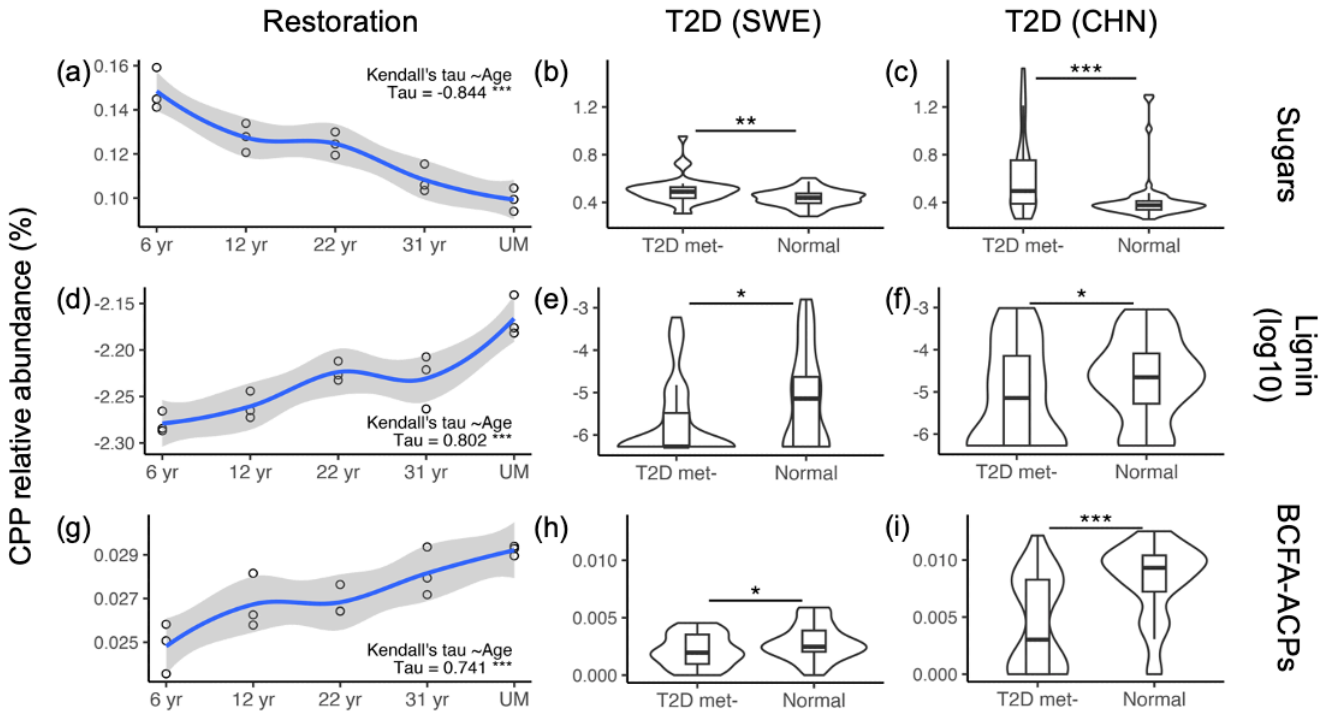

Figure 4. Potential metabolism of sugars (a-c), lignin (d-f), and branched-chain fatty acid – acyl carrier proteins (BCFA-ACPs, listed in Tables S3, S4) (g-i), within the restoration gradient (spanning restoration planting ages 6, 12, 22, 31 years and unmined, UM) (a, d, e), T2D (Swedish cohort, SWE; T2D met- = type 2 diabetes not treated with metformin, Normal = normal healthy subjects) (b, e, h), and T2D (Chinese cohort, CHN) (c, f, i). Sugars and BCFA-ACPs were groupings identified via matching trends in T2D (SWE) and with ecosystem degradation (Figure 3). Sugars were graphed as the sum of compound processing potential (CPP, %) for six compounds (L-arabinose, melibiose, D-fructose, sucrose, manninotriose and D-lyxulose), however subsequent testing showed only three of these sugars (L-arabinose, melibiose, D-fructose) displayed individual trends in T2D (Chinese cohort, CHN) (Tables S2, S4). Lignin CPP values were $\log_{10}$-transformed to improve display.

395 To confirm and consolidate individual compound trends exhaustively across all compound-wide
396 trend results, we further isolated only those ModelSEED compound identifiers with matching trends
397 across all three case studies. This process identified 76 compounds with n = 60 decreased, n = 16
398 increased with ecosystem degradation, T2D (SWE) and T2D (CHN) (Figure 5; Table S4; compound
399 and trend data are further detailed in Supplementary Material). Summary trend and contextual
400 information are displayed in Figure 5, using mean results from T2D (SWE) and T2D (CHN) cohort
401 datasets. From this filtering process at the individual compound level, remarkably, the signal of
402 decreased potential metabolism for all 35 compounds in the BCFA-ACPs group previously identified
403 from overlapping restoration gradient and T2D (SWE) datasets also remained when intersected with
404 the T2D (CHN) dataset.

405 The BCFA-ACPs group comprised three categories of compounds: monomethyl unsaturated
406 medium to long BCFA-ACPs (n = 18), monomethyl saturated predominantly medium BCFA-ACPs (n
407 = 12), and unsaturated short, medium, and long straight-chain fatty acid-ACPs (n = 5) (Table S3).
408 BCFA lengths are based on the main carbon chain (short: < 6, medium: 6-12, long: 13-21 carbon
409 atoms; Mao et al., 2023). All 35 compounds, for all case studies, were associated with NADH and
410 NADPH enoyl-ACP reductases (EC 1.3.1.9 and EC 1.3.1.10 respectively), while several compounds
411 from the restoration case study were also associated with beta-ketoacyl-ACP synthase (EC 2.3.1.41) –
412 all of which are involved in type II fatty acid biosynthesis. One compound from the BCFA-ACPs group
413 (unsaturated medium-length straight-chain (2E)-Decenoyl-[acp]) was also associated across all case
414 studies with trans-2-cis-3-decenoyl-ACP isomerase (EC 5.3.3.14), which is involved in unsaturated
415 fatty acid biosynthesis.

416 As monomethyl BCFA-ACPs dominated this trend group, we were curious to understand
417 whether they might feature there exclusively, or if similar compounds were also present throughout the
418 data and not display trends. We found hundreds of other unique non-trending ACP-containing

419 compounds (*n* = 296 restoration, *n* = 289 T2D-SWE, *n* = 293 T2D-CHN), spanning a multitude of
420 enzymes or sub-functions (*n* = 223 restoration, *n* = 137 T2D-SWE, *n* = 146 T2D-CHN). Focusing only
421 on the methyl-containing variants, a shared inventory of non-trending ACP compounds was found
422 across all three datasets. Intriguingly, there were no other monomethyl unsaturated (-enoyl) BCFA in
423 the datasets beyond those that featured in our BCFA-ACPs trend group. The remaining shared non-
424 trending methyl-containing ACP compounds (*n* = 56) either contained carbonyl (-oxo-) groups (*n* =
425 18), or hydroxyl (-hydroxy-) groups (*n* = 22), or ester groups (*n* = 9), while the remaining (*n* = 7) were
426 saturated BCFA-ACPs (one short chain, and six long 13-16 chain length). These latter, non-trending
427 saturated BCFA-ACPs also differed from the saturated BCFA-ACPs in our trend group, which
428 contained mostly medium-length chains (Table S3).

429 Additionally, when results from the T2D (CHN) dataset were intersected, this refined the results
430 for the sugars that were previously highlighted from overlapping the restoration gradient and T2D
431 (SWE) datasets. When all datasets were intersected, arabinose, fructose, and melibiose still remained as
432 trending, together with 6-phosphosucrose, an intermediate in sucrose biosynthesis.
433

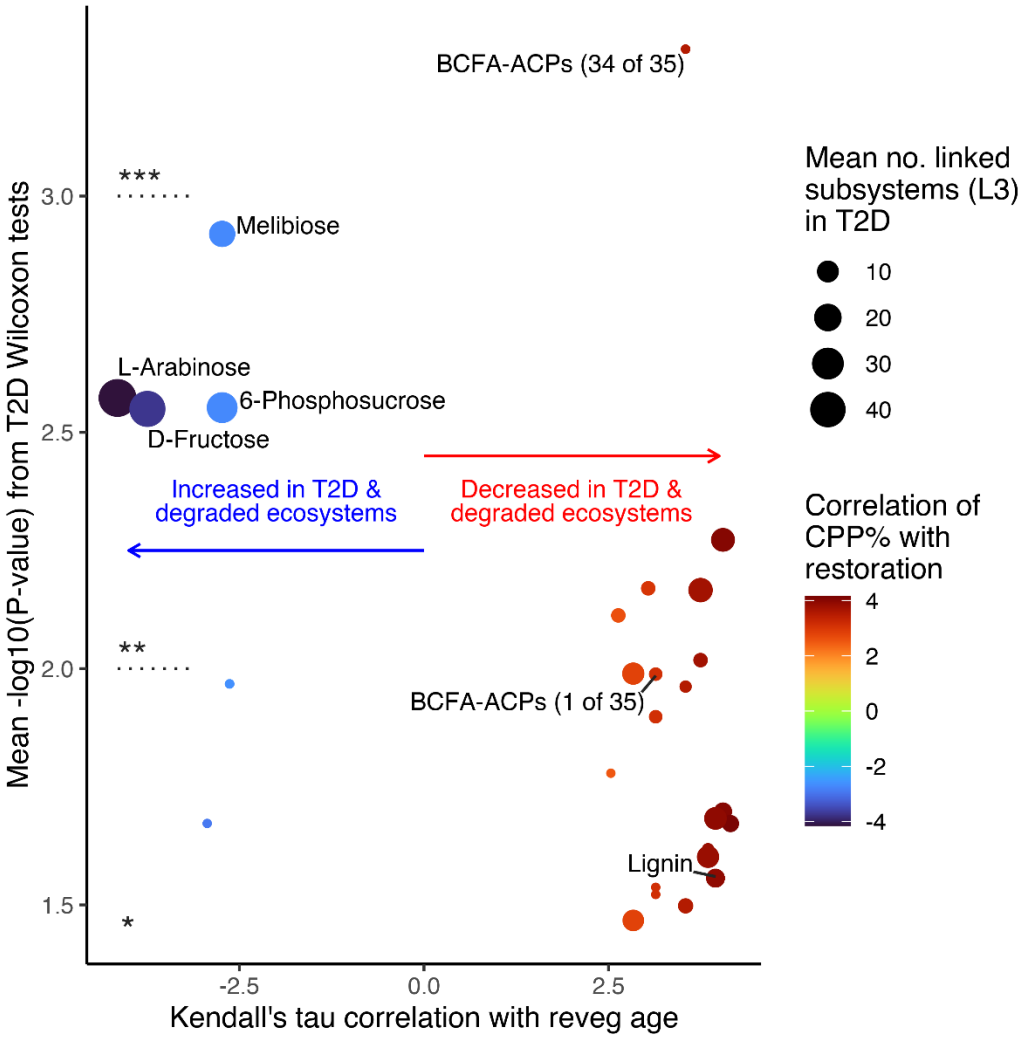

Figure 5. Relative importance of compounds with consistent trends across all case study data, showing increased or decreased compound processing potential (CPP %, i.e., potential metabolism) with ecosystem degradation (soil) and in T2D (gut) microbiomes. Compounds including branched-chain fatty acid-acyl carrier proteins (BCFA-ACPs), sugars that feature widely across many functional themes and pathways, and lignin are highlighted in the plot. Trends with ecosystem degradation are interpreted as the inverse of restoration (based on Kendall's tau ordinal correlation with revegetation age classes). Measures of significance (y-axis) from the Wilcoxon difference testing of CPP in T2D (versus normal), and the number of level 3 (L3) subsystems (functional themes) linked to each

443 compound, are calculated as mean values from the Swedish and Chinese cohorts. Further details for
444 compounds (n = 76 total) are in Table S4.
445

446 ## 4. Discussion

447 We identify several meaningful overlapping trends in the functional capacity of soil and human gut
448 microbiomes, supporting our hypothesis that increased population exposure to degraded soil
449 ecosystems may contribute to the development of type 2 diabetes. These linkages warrant further
450 investigation due to the rising prevalence and impact of T2D and the widespread and increasing
451 processes of global change impacting soil microbiomes, which provide a key reservoir and source for
452 priming and resupplying the human gut microbiome. A possible alternative or complementary
453 explanation may be that similar ecological stresses and dysfunction in soil and gut ecosystems may be
454 driving convergence in microbial functional traits. Using a novel method, we translated community-
455 scale microbial metagenome functional capacities to quantify potential metabolism for individual
456 compounds. This compound-oriented approach facilitates linkages to a wealth of published literature
457 that links chemical compounds with metabolism, health and wider biological processes in humans and
458 the environment. Our mapping of compounds into the bioenergetically informed O:C, H:C and N:C
459 coordinate space helped to reveal meaningful patterns of simultaneously trending compounds (e.g.,
460 sugars, BCFA-ACPs) with soil-ecosystem quality and T2D versus normal health.
461

462 ### 4.1. Do branched-chain fatty acids connect healthy ecosystems and healthy people?

463 Our data suggest that microbiomes in degraded ecosystems and T2D have reduced capacity for
464 monomethyl BCFA (mmBCFA) biosynthesis. This may reflect a shift in the biochemical composition
465 of bacterial assemblages as BCFAs are key components that enhance bacterial membrane fluidity, and
466 BCFA synthesis capacity enables membrane fluidity-related adaptive responses for survival and

467 proliferation through environmental stresses (Gozdzik et al., 2023; Yoon et al., 2015). BCFA levels
468 vary among bacterial taxa, being commonly higher in Gram-positive bacteria, present in some Gram-
469 negative species, and especially high in *Bacillus* and *Bifidobacterium* (Yang et al., 2025; Yoon et al.,
470 2015). Within ecosystems, BCFAs are present in lipid/waxy plant compounds, animal (including
471 human) tissues and fluids, including ruminant products (milk, cheese, meat), fish, organs, blood serum,
472 skin, hair, adipose tissue, colostrum, breast milk, *vernix caseosa* of newborns, and at very high levels in
473 saprotrophic fungi such as *Conidiobolus* spp. found in soil and decaying organic matter (Gozdzik et al.,
474 2023; Maheshwari et al., 2020; Mao et al., 2023). Therefore, variation in BCFA synthesis capacity
475 could result from changes in microbial taxonomic composition as ecosystems degrade.

476 Monomethyl BCFAs are of interest because they possess multiple beneficial bioactivities for
477 human health and provide a direct link between bacterial and human physiology (Mao et al., 2023).
478 Beneficial bioactivities of mmBCFA include lipid-lowering, reducing the risk of metabolic disorders,
479 maintaining normal β cell (i.e., insulin-producing) function and insulin sensitivity, anti-inflammation,
480 cytotoxicity to cancer cells and regulation of development (Gozdzik et al., 2023; Mao et al., 2023;
481 Yang et al., 2025). Bacterially-derived mmBCFAs facilitate the direct biochemical crosstalk (i.e.,
482 uptake and cross-domain metabolism) between the gut microbiome and animal hosts (Brown et al.,
483 2023; Zhu et al., 2013; Zhu et al., 2021). In the nematode *Caenorhabditis elegans* and mammalian
484 tissue culture cells, mmBCFA have been shown to trigger the host mechanistic target of rapamycin
485 complex 1 (mTORC1) (Zhu et al., 2013; Zhu et al., 2021), a central regulator of cell growth and
486 metabolism (Takahara et al., 2020). The host mTORC1 responds to environmental signals (e.g., amino
487 acid availability, growth factors, energy levels, stress) to coordinate cellular status. However, mTORC1
488 dysregulation is closely linked to diabetes, cancer, and neurodegenerative disorders (Takahara et al.,
489 2020). Liu et al. (2017) reported high capacities for human fetal intestinal epithelial cells (enterocytes)
490 to incorporate long-chain BCFA into membrane phospholipids. Following uptake by human intestinal

epithelial cells, further potential interactions between BCFA and host endogenous BCFA synthesis and metabolism may occur (Gozdzik et al., 2023; Mao et al., 2023), including post-translational modifications to cell proteins, which alter intestinal cell function (Ezzine et al., 2022). While the precise mechanisms are uncertain, it is plausible that mmBCFA in the gut microbiome might modulate host cellular metabolism and physiological functioning via these interactions.

Microbial sources play a dominant role in the supply of health-associated mmBCFA (Mao et al., 2023; Yang et al., 2025). Key inputs to BCFA synthesis include branched-chain amino acids (which can only be made in bacteria, plants, and fungi, but not in animals; Neinast et al., 2019) or shorter BCFA, which can be elongated. Microbes (e.g., rumen bacteria) also contribute to BCFA synthesis in animals (Mao et al., 2023). Subsequently, both diet and gut microbiome synthesis provide major sources of BCFA to humans (Mao et al., 2023; Yang et al., 2025). Within microbial environments (e.g., in soil or the gut), the interchange of BCFA between substrates and microbes can be expected because fatty acids are a high-value energy source, and bacteria can assimilate environmental BCFA into their bodies (Sen et al., 2016; Yao & Rock, 2015). In the gut, the constant release of a portion of mmBCFAs from bacterial cell membranes occurs due to the rapid turnover of bacterial cells from competitive interactions (Booth et al., 2023) and the secretion of fatty acids and their derivatives (Brown et al., 2023). A portion of these gut bacteria may be supplied from external ecosystem exposures (Roslund et al., 2021; Rothschild et al., 2018) and be further shaped by diet and other factors (e.g., high BCFA-content Bifidobacterium spp. proliferate in infants receiving breast milk; Stewart et al., 2018).

As ecosystems degrade, there may be several reasons why BCFA-synthesizing organisms decline. Ecosystem degradation is widely associated with reductions in soil organic matter (e.g., Chen et al., 2018; Cunningham et al., 2015; IPBES, 2018; Kooch et al., 2022). Indeed, the more degraded soils from the restoration gradient case study dataset had lower soil organic content than unmined sites (Avera et al., 2015). Soil organic matter comprises a continuum of progressively decomposed organic

515 compounds originating from plant residues, root exudates, microbial synthesis, and other chemical
516 reactions, and commonly includes amino acids and fatty acids (Song et al., 2024). Amino acids can be
517 released from proteins in the soil through proteolysis at rates correlated with soil organic matter pools
518 and soil protein concentrations (Näsholm et al., 2009). This release increases with ecosystem
519 succession (Kielland et al., 2007). Natural decomposition and recycling networks of saprotrophic fungi
520 (which includes many high BCFA-content spp.) may also be degraded, likely reducing BCFA content
521 and turnover in soil microbiomes. Diverse plant litter contributes to increased soil carbon, higher
522 microbial abundance, diversity, decomposition and turnover, which strengthens over time (Zhang et al.,
523 2023). In contrast, urban areas exhibit dramatically reduced fungal abundance and diversity compared
524 to natural ecosystems (Abrego et al., 2020). Urbanization has been associated with the homogenization
525 of soil microbiomes (Delgado-Baquerizo et al., 2021), which in turn reduces the diversity of
526 assemblages that resupply the human gut microbiome. Taken together, these influences may reduce
527 access to and recycling of both branched-chain amino acids and fatty acids for soil microbiomes in
528 degraded ecosystems, thereby potentially reducing ambient human exposure to health-promoting
529 microbial BCFA synthesis capacity.
530

531 **4.2. Identified compounds linked to energy harvesting**

532 We found that potential metabolism of sugars (including arabinose, fructose, and melibiose) and the
533 intermediate compound 6-phosphosucrose each increased with ecosystem degradation and T2D.
534 Additionally, the potential metabolism of sucrose, glucose, galactose, xylose and mannose increased in
535 more degraded ecosystems. Sugars are the most abundant organic compounds in the biosphere and are
536 key carbon and energy sources for soil microbes (Gunina & Kuzyakov, 2015). Sugars in soil can either
537 be derived from primary sources (e.g., decomposition of plant litter, rhizodeposits, root exudates) or
538 secondary sources (e.g., microorganisms and their residues) (Gunina & Kuzyakov, 2015). Our

539 detection of increased potential metabolism of simple sugars (largely monosaccharides and
540 disaccharides) likely reflects enhanced microbial decomposition of soil organic matter within more
541 degraded, less biodiverse ecosystems (Chen et al., 2018). Aligning with the sugars that we identified,
542 previous work suggests that galactose, glucose, mannose, arabinose and xylose are chief components of
543 the estimated 5% sugar residues contained within soil organic matter (Nagar, 1962). We might
544 therefore conclude that increased potential metabolism of sugars is indicative of microbiomes in
545 degraded ecosystems that consume, rather than build or maintain, soil organic matter.

546 In the gut microbiome, carbohydrate metabolism contributes up to 10% of the host's overall
547 energy extraction and is recognized as an important contributor to insulin resistance and the
548 development of obesity and prediabetes (Takeuchi et al., 2023). Takeuchi et al. (2023) found increased
549 gut microbiome metabolism of monosaccharides, including fructose, galactose, mannose and xylose,
550 significantly correlated with insulin resistance. Interestingly, in soils and humans, enhanced sugar
551 metabolism is also associated with more opportunistic bacteria (Le Bouguénec & Schouler, 2011).
552 Increased relative abundances of opportunists (including fast-growing, potential pathogens) have been
553 associated with disturbance in urban greenspace soils (Delgado-Baquerizo et al., 2021) and in human-
554 altered land uses (Liddicoat et al., 2019). If microbial assemblages with enhanced sugar metabolism are
555 transferred from degraded ecosystems to the human gut, they may exhibit opportunistic or pathogen-
556 like traits—potentially contributing to increased energy harvest and metabolic imbalances associated
557 with T2D.

558

559 **4.3. Identified compounds linked to energy management**

560 We found altered potential metabolism for compounds with plausible links to energy management
561 (e.g., energy storage via fatty acids, gut hormone secretion and appetite regulation) that decreased in
562 both degraded ecosystems and T2D. This finding supports the notion that exposures to degraded

563 ecosystem soils that are deficient in potential metabolism of compounds involved in energy
564 management may supplement and shape gut microbiomes that are also deficient in this way, thereby
565 contributing to further metabolic imbalances found in T2D. We discuss above how gut microbiome
566 mmBCFA content and biosynthesis capacity might modulate host cellular metabolism via central
567 mTORC1 regulation, alteration of enterocyte phospholipid composition and function, and/or supply of
568 BCFA for further host endogenous fatty acid synthesis and BCFA-mediated metabolism.
569 Dietary fiber, such as lignin, is known to decrease plasma ghrelin, known as the hunger
570 hormone, and increase other key gut regulatory hormones: cholecystokinin (CCK), glucagon-like-
571 peptide-1 (GLP-1), and peptide YY (PYY) (Bulsiewicz, 2023). Short-chain fatty acids (SCFAs) are
572 produced when certain members of the gut microbiome ferment non-digestible fibers, and these SCFAs
573 bind to receptors in the colon, leading to the production of a range of key hormones that regulate food
574 intake, body weight, and energy metabolism (Bulsiewicz, 2023; Chao et al., 2025). We included both
575 lignin and pectin to represent fiber, which were detected in the datasets and are among the recognized
576 key types of dietary fibers (Blanco-Pérez et al., 2021). Potential metabolism of lignin decreased with
577 ecosystem degradation and in T2D gut microbiomes. Similar trends appeared for sinapyl alcohol and
578 coumaryl alcohol (both precursors to lignin) in the compound-wide results spanning all datasets.
579 Potential metabolism for pectin also decreased in T2D (significantly in the Swedish cohort, and
580 marginally in the Chinese cohort), but not in degraded ecosystems. We also searched for
581 oligosaccharides (e.g., fructan, inulin, galactan) but did not detect these compounds in our datasets.
582 Additional compounds that we identified remain to be explored (see Table S4).
583

584 **4.4. Disentangling dietary and environmental influences on T2D gut microbiomes**

585 We expect that our results showing altered potential metabolism for compounds detected within gut
586 metagenomes may arise from a combination of environmental exposures that supplement and shape gut

587 microbe assemblages, dietary choices that further support or deplete members of the gut microbiome,
588 gut environment and function, and neurological influences, among other factors (Cryan et al., 2019).
589 Where we found matching trends across all case studies (e.g., arabinose, fructose, melibiose, BCFA-
590 ACPs, lignin), this is consistent with an alignment between environmental exposures and dietary
591 choices or perhaps an overwhelming influence from environmental exposures. In the scenario where
592 compounds consistently showed in both T2D cohorts, but not in the restoration gradient, this suggests
593 dietary effects alone. For example, increased potential metabolism results for amylopectin and amylose
594 suggest that excessive consumption of starch-rich foods may contribute to T2D. For many compounds
595 we found alignment in potential metabolism between the ecosystem condition and T2D gut (Chinese
596 cohort), but not the T2D gut (Swedish cohort) – this may point to greater environmental exposures and
597 detrimental health influence in some population groups. Yet another contrast occurred in the case of
598 ammonia, where potential metabolism trends were opposing in the T2D cohorts, in the absence of any
599 ecosystem condition effect, which suggests a lone influence of dietary exposures associating with T2D.
600

601 **4.5. Implications for community connection to soils and ecosystems**

602 Our findings suggest that filling knowledge gaps in the pathogenesis of T2D may require more holistic
603 consideration of linkages, especially at the systems level of health risk and promotion (consistent with
604 Handte-Reinecker & Sardeshpande, 2025); such as where landscape-scale ecosystem management may
605 drive changes in microbial functional capacities represented across assemblages of organisms. Our
606 findings suggest that maintaining balanced functioning healthy soil ecosystems in human habitats,
607 especially those used for food production, is increasingly important for supporting healthy human
608 populations. Increasing urbanization, ecosystem degradation, the industrialization of food production
609 and its distribution, and reducing time spent in nature have collectively reduced contact with soil
610 microbiomes for a large proportion of people. When humans are exposed to soil in modern

environments, it is increasingly within urbanized or highly modified landscapes (e.g., degraded ecosystems with low natural biodiversity, highly modified land and disturbed soils, monocultural agricultural fields) where microbiomes and their functional capacities have been greatly altered.

From a societal viewpoint, our findings suggest that addressing the global T2D pandemic may benefit from restoring urban biodiversity, developing effective approaches for regenerative agriculture, increasing soil biological health and diversity as key parts of a restorative continuum, and finding a better balance between anthropogenic land use and nature. At the heart of this challenge lies the need for a deeper understanding of soil health—recognizing soil as a complex living ecosystem in which the microbiome plays a pivotal role. Understanding the critical links between soil health, food production, and human health is fundamental for strengthening the diminished connections between people, land and soil (Wall et al., 2015) and provides a foundation for developing strategies and actions that might lead to improved gut health and resilience to T2D. This critical understanding of links between soil ecosystem health and human health also draws on parallels of thinking about nature from an Indigenous peoples' worldview. Indigenous knowledge offers guidance and support to theories that place the health or condition of nature (land, biodiversity, water and air) as essential to maintaining human health and wellbeing. Central concepts also recognize the importance of reconnecting with nature by strengthening engagement with ecosystems through activities such as restoration and regeneration. For example, in Aotearoa-New Zealand, Indigenous Māori stress connection and inter-dependency with ecosystems through core principles such as ancestral links and association (Warbrick et al., 2023). This includes concepts of whakapapa (genealogical descent of all living things) which holistically reaffirms the importance of genetic and chemical assemblages in soils and landscapes to support all life forms, including microbiomes (Harmsworth & Awatere, 2013). Concepts of kaitiakitanga (guardianship of the environment) are also commonly used to reinforce actions and strategies to guide environmental restoration and promote health. Indigenous perspectives offer

important guidance to all peoples for personally reconnecting and engaging with our ecosystems and their stewardship in order to support healthy landscapes, soils, microbiomes and people.

4.6. Conclusions

We found overlapping trends in the potential metabolism of compounds with beneficial bioactivities and involved in energy harvesting and management within separate model case study datasets of degraded ecosystem soil and T2D gut microbiomes from Swedish and Chinese cohorts. Our results support existing studies implicating, at least in part, a role for microbiomes in T2D. Additionally, our findings support the hypothesis that excessive soil microbiome exposures from degraded environments may contribute to metabolic imbalances found in T2D. Our novel method used to examine microbiome potential metabolism at the resolution of individual compounds has derived new insights into potential links between soil, ecosystem and T2D gut health that warrant further transdisciplinary investigation.

Data availability

Code used to support this study is available from: https://github.com/liddic/cpp3d_t2d

Acknowledgments

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