Gut microbiome associations with diet and medication usage in type 2 diabetes

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INTRODUCTION

The gut microbiome is essential for human health, and disturbed microbial communities have been associated with a broad range of medical conditions. However, it has proven difficult to identify detailed, disease-specific microbial features that are robust across populations. This limitation is partially due to the high variability of the gut microbiome, likely due to as-yet-uncaptured environmental influences. In the current study we evaluate the importance of medication and food supplements in relation to microbial studies of obesity and type 2 diabetes (T2D). See **Figure 1** for overview of study cohorts.

RESULTS

We identified strong effects of commonly used medications as well as dietary components (minerals and vitamins). Five main drug classes showed strong effects on the microbial composition (**Table 3**). Similarly, we analyzed the effect of five commonly used food supplements, and found all to be significantly associated with either abundance or functional composition of the gut microbiome (q-value < 0.1). When we considered the correlation of selected nutrients and food groups (assessed by FFQ) with variance in gut microbial composition (BC dissimilarity) we found high-energy variables, and vitamins and minerals, most associated (**Figure 2**). However, age and gender were the variables most strongly associated to BC dissimilarity, while the overall variance explained was restricted to 1.44% for genera across lean non-diabetic samples, including 24 nutritional variables.

CONCLUSION

The associations of gut microbial features with food supplements and medication intake are of interest both as a source of confounding effects when studying the microbiome and health outcomes, and for their potential direct clinical relevance. Our findings thus emphasize the need to profile these environmental covariates, along with demographic and biometric factors, in population studies of health outcomes.
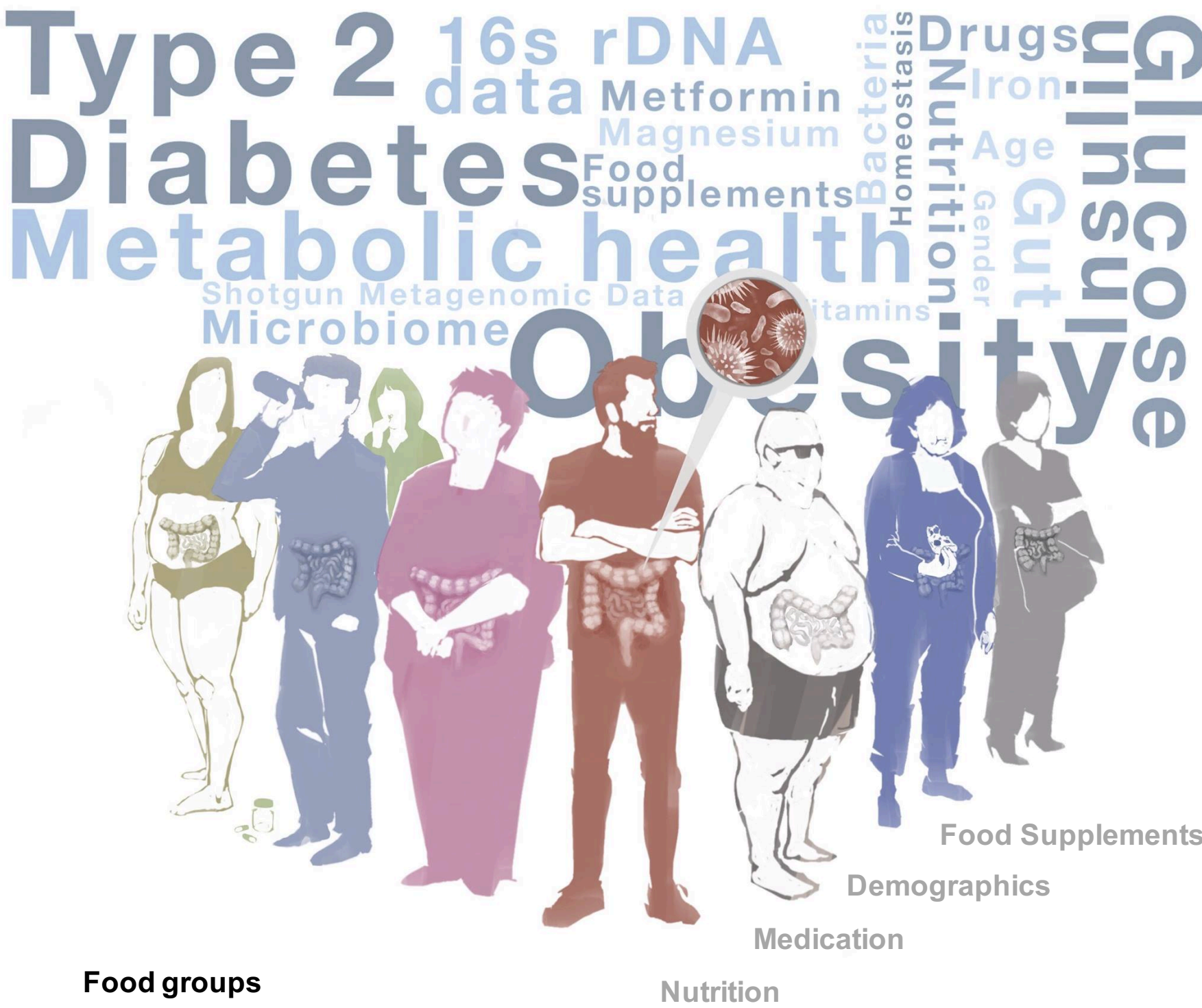

Figure 1 (above): Overview of study samples, health outcomes and factors of the gut microbial environment considered in the study. We analyzed 1,304 stool-derived amplicon profiles and 154 shotgun metagenomes from two samples from Northern Germany (cross-sectional cohort from PopGen & both cross sectional and clinical samples from FoCus). Findings for medication usage were validated in 880 samples from North-eastern Germany (SHIP). Three phenotypic groups were considered in the study: Lean non-diabetic, obese non-diabetic and obese type 2 diabetic (T2D) individuals. Environmental factors considered in the analysis include medication usage, general measures of health and fitness, nutrition and food supplement usage, and demographic factors. (Illustration by Sigurd Thingholm).
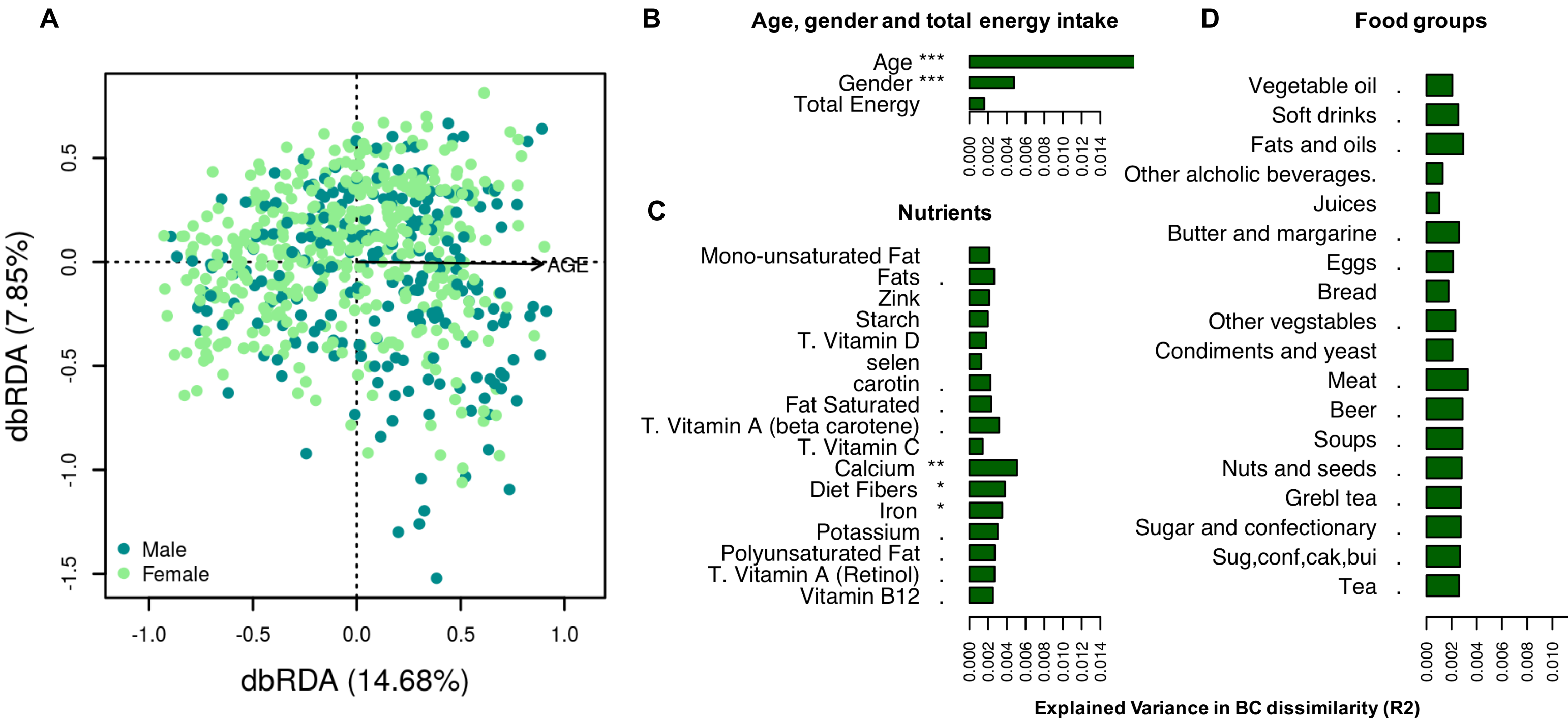

Figure 2 (above): Association of age, gender and nutrition with gut microbiome composition. Panel (A) shows the association of age and gender with the first two unconditioned dbRDA axis (Capscale in R/Vegan) of gut microbiome relative abundance data. Axis labels show percentage variance explained calculated as axis eigenvalues proportion of total eigenvalues. Panels (C) and (D) show top nutrients and food groups associated with gut microbiome composition (Adonis in R/Vegan, . = 0.1-0.2; * = 0.05-0.1; ** = 0.01-0.05; *** ≤ 0.01). Age and gender associated significantly with the microbiome composition, while total energy intake showed limited association (panel A and B). The individual nutrition-derived variables explained limited variance in gut microbiome composition, compared to age and gender. The plot include non-diabetic lean samples with 16S rDNA data analyzed at genera level. T. indicate variables were daily intake is calculated from both nutrition and food supplements. BC: Bray-Curtis dissimilarity. Grebl tea: Grey and black tea. Sug,conf,cak,bui: sugar, confectionary, cakes and biscuits.

Food Supplements		Drug Classes				
PopGen & FoCus		**PopGen & FoCus**			**SHIP**	
p-value	BH adjusted p-value		p-value	BH adjusted p-value	p-value	BH adjusted p-value
Genera			**Genera**			
Magnesium — 2.60×10-04	3.70×10-04	Antihypertensives	5.60×10-05	1.40×10-04	2.24×10-07	1.12×10-06
Vitamin and minerals — 2.10×10-04	3.70×10-04	Analgesics	2.08×10-04	3.47×10-04	1.87×10-05	3.12×10-05
Vitamin C — 2.80×10-04	3.70×10-04	Antidepressants	4.80×10-03	4.80×10-03	3.33×10-02	3.33×10-02
Calcium — 1.03×10-03	1.00×10-03	Antiphlogistics	1.02×10-03	1.28×10-03	7.06×10-05	8.83×10-05
		Antidiabetics	2.16×10-05	1.08×10-04	1.10×10-05	2.75×10-05
Pathways			**Pathways**			
Magnesium — 8.00×10-04	3.20×10-03	Analgesics	7.12×10-06	1.19×10-05		
Vitamin and minerals — 5.60×10-03	1.10×10-02	Antidepressants	1.18×10-04	1.48×10-04		
Vitamin C — 1.60×10-02	1.60×10-02	Antihypertensives	2.20×10-08	5.65×10-08		
Iron — 1.30×10-02	1.60×10-02	Antiphlogistics	0.00116	0.00116		
		Antidiabetics	2.26×10-08	5.65×10-08		

Table 1: Five drug classes and food supplements evaluated for association with microbial composition. Linear discriminant analysis (LDA) with the first 10 principal components (PCoA, Bray Curtis dissimilarity, 16S rDNA data at genera level or metagenomic pathway abundance data) was used to evaluate the difference in microbial composition between users and non users of each drug class or food supplement. Raw and Benjamini-Hochberg (BH) adjusted p-values are shown for analyses on Northern German cohorts (PopGen and FoCus) and North-eastern German cohorts (SHIP).