

HYPOTHESIS

Are noncommunicable diseases communicable?

Numerous noncommunicable diseases could have a transmissible microbial component

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The past century has seen a profound decrease in mortality rates across the world, accompanied by a marked shift from communicable diseases (caused by infectious microbes) to noncommunicable diseases (NCDs) such as cardiovascular diseases, cancer, and respiratory diseases. NCDs—defined as diseases that are not transmissible directly from one person to another—account for more than 70% (41 million) of all deaths globally (1). The definition of NCDs rules out microbial involvement and instead focuses on genetic, environmental, and lifestyle factors. Data increasingly show that the microbiota is dysbiotic (altered) in individuals with various NCDs. In animal models of NCDs, transplantation of dysbiotic microbiota into healthy animals results in disease, and microbiota composition is shaped by close contact with others. Therefore, we propose that some NCDs could have a microbial component and, if so, might be communicable via the microbiota.

Infectious diseases are caused by the transmission of pathogens between individuals. However, the extent to which microbial dispersal between humans contributes to NCDs remains unclear. The human microbiota consists of the various microbes (including bacteria, fungi, and viruses) living in and on the human body and has an important role in many physiological functions, including digestion, immune responses, and metabolism. Although microbes reside on many body sites, the majority are in the gut, with bacteria being the most studied. Several examples of NCD transmission exist by fecal microbiota transplant (FMT) into animal models, but how transmissible is the human microbiota? Cohabitants and spouses have more similar gut bacterial microbiota than genetically similar siblings living separately. Microbiota are transmissible within both family and social networks, and spousal relationships can be determined on the basis of gut bacterial analysis (2). Because families share diets and

environments, their microbiota is expected to be similar. Thus, whether shared microbiota influence the transmissibility of NCDs is challenging to investigate, because uncoupling environment from microbiota is difficult.

Obesity is a leading risk factor for many NCDs, and there is increasing evidence that obesity has a microbial component. FMT from genetically predisposed or diet-induced obese animals to germ-free, lean animals causes significant weight gain (3), indicating that gut microbes are part of the etiology. The risk of postdieting weight regain in formerly obese mice is increased by a persistently altered gut microbiota, which is transferable to germ-free mice (4). Studies suggest that obesity may also be communicable in humans. In a social network study of 12,067 people over 30 years (5), having an obese friend was associated with a 57% higher chance of being obese, and there was a 40% higher chance of obesity if a sibling was obese. Moreover, a study of U.S. military families showed that being stationed in a county with high obesity rates was associated with an increased body mass index (BMI), whereas those stationed in counties with lower obesity rates had a lower BMI (6). These data are consistent with the idea that a socially transmissible component contributes to obesity, representing a shared environment, including diet and lifestyle, as well as microbiota. However, it is difficult to uncouple environment (diet, social habits) from microbiota composition, because they are intimately connected. Currently, microbial transmission of NCDs has only been demonstrated in controlled FMT experiments in genetically similar animal models with the same diets and environments.

Obesity is the highest risk factor for type 2 diabetes (T2D). Thus, the risk for developing T2D may also have a communicable component through the microbiota. Within a year of a T2D diagnosis, spouses have a higher chance of developing T2D, and this trend remains over 3 years after the initial diagnosis. In mice, T2D has a microbially transferable component, as demonstrated by FMT from mice with T2D into germ-free mice (7). Inflammatory bowel diseases (IBDs) are associated with characteristic dysbiotic microbiota, which can be transferred from diseased humans or mice to healthy animals along with the disease phenotype (8). Spouses of IBD patients have similar dysbiotic microbiota compositions and a higher rate of disease than

accounted for by chance alone, although, like most infectious diseases, the “transmission” rate is not 100%. In India, the rate of ulcerative colitis (UC) is low, yet after moving from India to the United Kingdom, United States, and Canada, migrants have higher levels of UC. This change is attributed to “environmental factors,” including diet and lifestyle, and the gut microbiota could be a contributing factor. Host genetic predisposition to IBD, and thus individual physiology, also plays a role, with more than 200 genetic loci linked to IBD (9). Many of these, such as *NOD2* (nucleotide-binding oligomerization domain-containing 2), are linked to immune functions that affect the gut microbiota composition, emphasizing the link between host genetics and the microbiota.

How can connections between transmissible microbiota and NCDs be tested? In 1890, Robert Koch published a set of postulates to determine whether a microbe was the cause of an infectious disease. Although exceptions exist, this set of “rules” has served well for establishing the causative agent of most infectious diseases. Applying a version of Koch’s postulates that are adapted to NCDs could determine whether the collective microbiota can be considered an “infectious agent,” which would support the hypothesis of communicable NCDs (see the figure). For these “microbiota-associated postulates,” dysbiotic microbiota is considered the pathogen or causative agent and is defined as being different from the microbiota composition of unaffected individuals. The first postulate states that the microorganism should be present in those with disease. A strong correlation exists between a dysbiotic microbiota and many NCDs, including cardiovascular disease (CVD) and IBD. The second postulate states that the organism can be isolated from a diseased host and grown in pure culture. Collectively, dysbiotic microbiota can be harvested from feces, and many members grown. The third postulate states that the microbe, when inoculated into a healthy organism, should cause disease. FMT of dysbiotic microbiota from individuals with various NCDs into healthy animals results in disease, such as CVD, IBD, T2D, and many others. The final postulate states that the microorganism be isolated from the diseased host. This has been well documented for dysbiotic microbiota for many animal models of NCDs (10).

These modified postulates can be applied

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to CVD (heart attacks and strokes), the most prevalent NCD worldwide. There are strong correlations with the prevalence of particular gut microbiota that encode the enzyme choline trimethylamine (TMA)-lyase (CutC) that metabolizes phosphocholine and carnitine (from red meat) into TMA, which then undergoes hepatic oxidation into trimethylamine oxide (TMAO) (11). The concentration of TMAO in the blood is a strong predictor of CVD, with higher prevalence of disease associated with the presence of CutC-encoding gut microbes (12). Germ-free animals do not acquire CVD, even if on a choline-rich diet, and vegans and vegetarians have lower CVD rates than meat eaters (13). If CutC is inhibited in animal models, CVD does not occur. Moreover, human gut microbes encoding CutC can be transplanted into animals, leading to CVD phenotypes (14). Research examining spousal or community rates of CVD have so far only examined environmental

effects (e.g., smoking, obesity, and alcohol). These may alter the gut microbiota composition, and so further research is warranted to examine whether microbial transmission is also involved.

Applying modified Koch's postulates to CVD therefore reveals a strong correlation with a dysbiotic microbial composition (prevalence of bacteria encoding the CutC enzyme) and TMAO production and CVD, which addresses the first postulate. These organisms can be grown in the laboratory, thus satisfying the second postulate, and then transferred into healthy animals, which results in CVD (14), thereby satisfying the third postulate. These CutC-encoding microbes can also be isolated and cultured from diseased animals, satisfying the fourth postulate.

Similarly, these modified Koch's postulates can be applied to obesity (although not an NCD, it is the leading risk factor for many NCDs) and to IBD. In both cases, a character-

istic dysbiotic microbiota can be introduced into animals, resulting in obesity or IBD. There are certainly caveats to this "proof" of causation and thus communicable NCDs. In particular, dysbiotic microbiota is not well defined and may differ in composition between individuals. Dysbiotic microbiota are associated to varying degrees with different NCDs—for example, they play a smaller role in cancer than in CVD. These analyses raise the hypothesis that transmissible dysbiotic microbiota contribute to NCDs in humans, but uncoupling this from environmental components and genetic predisposition will require substantial additional research.

These observations suggest that the microbiota could be a causal and transmissible element in certain diseases that have been traditionally classified as NCDs. It is hoped that this hypothesis stimulates additional discussion and research, including studies that define environmental effects on the microbiota, identifying microbial members that constitute a dysbiotic transmissible microbiota that confers disease, and further delineating the extent of the contribution of the microbiota to NCDs. Notably, transmissible microbiota, especially early in life, may also have a protective role against NCDs, including asthma, allergies, and obesity; these protective microbes can also be experimentally transmitted to animal models (15). Additionally, only gut bacteria have been considered in this discussion, yet viruses and fungi may also contribute to NCDs, as well as microbiota at other body sites such as the skin and oral cavity. As the potential role of transmissible microbiota in NCDs becomes better defined, it will provide new opportunities to address these complex diseases. ■

Transmission of dysbiotic microbiota

It is proposed that dysbiotic microbiota, particularly in the gut, can be transmitted to other individuals, in turn altering their microbiota. This may contribute to the spread of noncommunicable diseases (NCDs), including obesity, a key risk factor for many NCDs, as well as possibly cardiovascular disease and inflammatory bowel diseases.

Koch's postulates

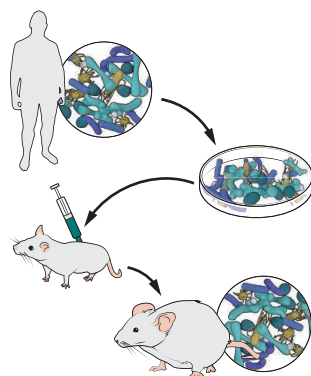
Suspected pathogen...

is found in individuals with communicable disease.

can be isolated from the host and grown in culture.

can cause disease when inoculated into a healthy host.

can be reisolated from the inoculated host.



Microbiota-associated postulates

Dysbiotic microbiota...

are found in individuals with NCD.

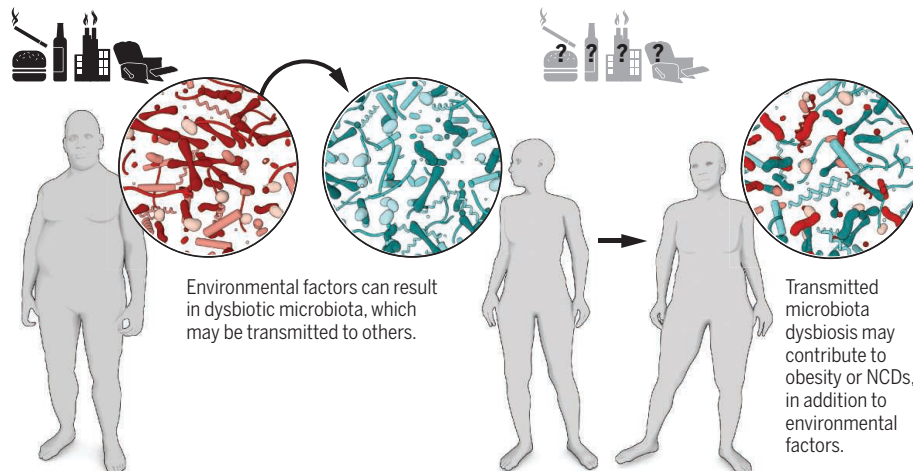
can be harvested and grown in culture.

can cause disease when transferred into a healthy host.

can be reisolated from the inoculated host.

Microbial transmission in NCDs?

The microbiota of an individual is affected by environmental factors such as diet, smoking, alcohol intake, and exercise. Dysbiotic microbiota can influence NCDs or their risk factors, such as obesity, and might be transmitted between individuals, potentially contributing to the spread of disease.



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