



# The hygiene hypothesis at a glance: Early exposures, immune mechanism and novel therapies



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## ABSTRACT

The hygiene hypothesis was proposed almost three decades ago. Nevertheless, its mechanism still remains with relevant controversies. Some studies defend that early exposures during childhood to microbes and parasites are key determinants to prevent allergies and autoimmune diseases; however, other studies demonstrated that these early exposures can even potentiate the clinical scenario of the diseases. Based on several studies covering the influences of microbiome, parasites, related theories and others, this review focuses on recent advances in the hygiene hypothesis field. In addition, the main immunological mechanisms underlying the hygiene hypothesis are also discussed. We also strongly encourage that researchers do not consider the hygiene hypothesis as a theory based strictly on hygiene habits, but a theory combining diverse influences, as illustrated in this review as the hygiene hypothesis net.

## 1. Introduction

Based on experimental evidence as well as epidemiological results, it is possible to verify the notable increasing incidence of allergic diseases during the last decades, especially on the western countries. Today, worldwide sensitization to foreign proteins (IgE produced-antibodies) is presented between 20–40% of the population. This worldwide allergy pattern involves anaphylaxis, food allergy, asthma, rhinitis, conjunctivitis, eczema, allergy to bug-bite and many others. According to the hygiene hypothesis, this allergy increase is caused due to low exposures to a wide array of infections, which present the ability to modulate the human immune system (Canonica et al., 2013; Jappe et al., 2017; Pawankar, 2014; Pawankar et al., 2011; Versini et al., 2015).

In this review, the current state of art of the hygiene hypothesis and its role on allergies, autoimmune diseases and other diseases will be discussed. Moreover, we will provide details on the hypothesis history, documented cases, the induced-immune-mechanism, the controversial studies, as well as the recent use of the theory to perform novel therapies.

## 2. The hygiene hypothesis

In 1989, David P. Strachan formulated a theory proposing that the development of infections during the first period of childhood decreases when there is non-hygienic contact with older siblings from the same family. Studying hay fever, a seasonal allergic rhinitis, Strachan observed the so-called post-industrial revolution epidemic, using 17,414 British children following them up for 23 years. A total of 16 variables divided between perinatal, environmental and social factors were analyzed. Thanks to his evaluation, it was able to find a solid association on the incidence of hay fever with family size and position in the household during the childhood. Thus, the hygiene hypothesis was formulated based on an inverse relation between the size of a household and the occurrence of atopic disturbs, suggesting that this theory could explain allergies.

Ten years after the original article about hygiene hypothesis, Strachan held another evaluation, this time covering both England and New Zealand. He studied the increase or decrease of average family size between 1961 and 1991, trying to correlate these results with the variation on the prevalence of hay fever on general population. The study demonstrated that family size alone was not enough to justify the elevation of hay fever prevalence, concluding that the household size was only one of the many risk factors that need to be studied, including

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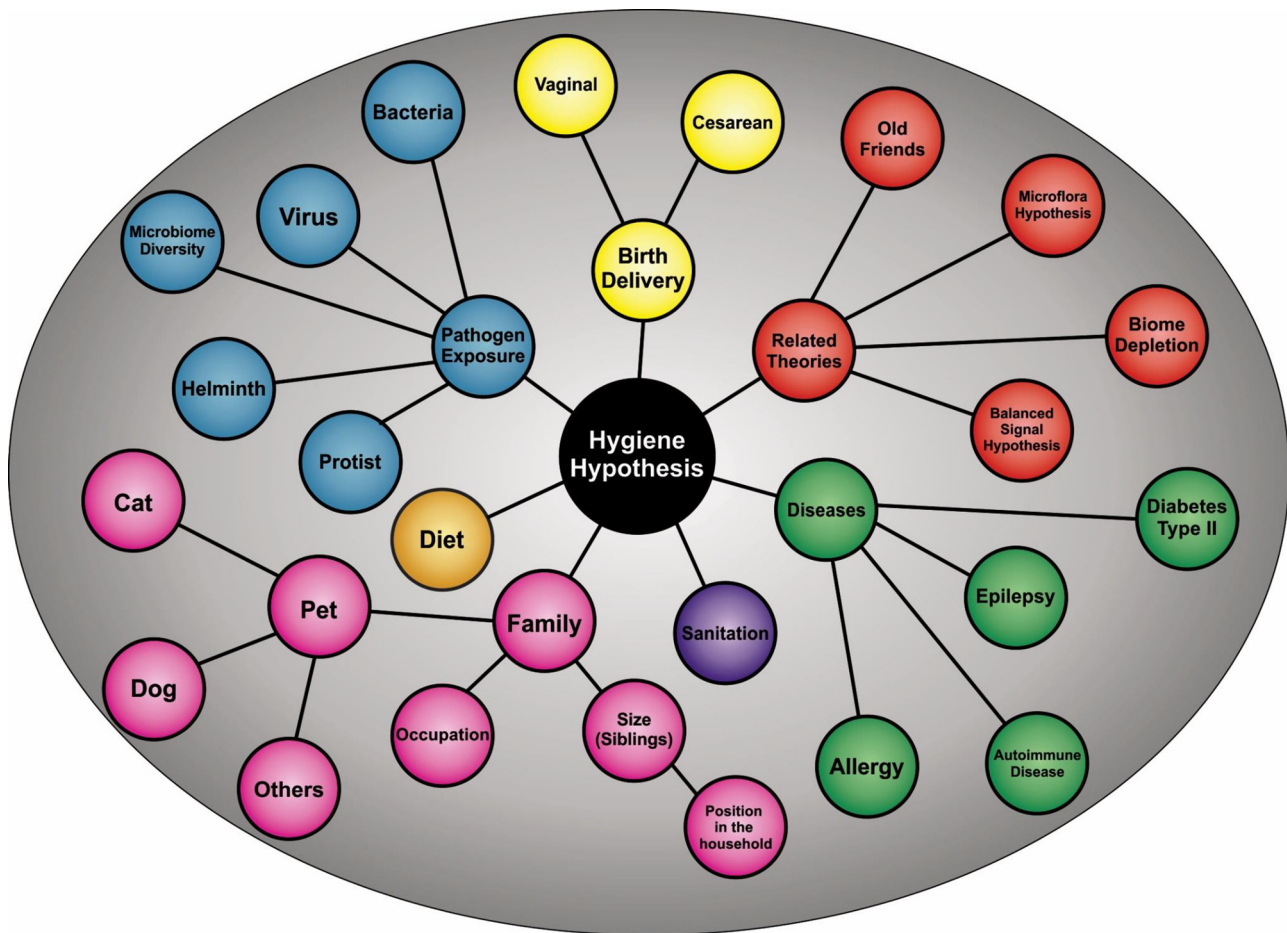


Fig. 1. The hygiene hypothesis net. The figure illustrates the main influences related to the hygiene hypothesis.

the incidence of infections (Bloomfield et al., 2006; Strachan, 1989, 2000). Following the hygiene hypothesis solidification and the use of its concept, immunologists and allergy specialists have been dedicated in understanding how exposure to antigens can be determining factors on the incidence of allergies, autoimmunity and even other diseases (Fig. 1).

From the time of hypothesis formulation to nowadays, the theory went through various modifications resulted from several studies, including the in-depth knowledge regarding immune system mechanisms and T helper cells (Th) populations (Th1, Th2, Th17 and T regulatory cells - Treg), the description of interleukins produced by these cells (e.g. INF- $\gamma$ , IL-4, IL-17, IL-10, TGF- $\beta$ ), and the increased studies concerning the rich microbiome, cycles of parasites and infections in general. Indeed, many questions are still unanswered concerning how microbiome and parasites can modulate the human immune system; however, many advances were already reached.

Operating in synergism with the hygiene hypothesis, the *old friends* theory is based on the principle that many microbes co-evolved with humans and, since microbes had to be tolerated, they developed strategies to induce modulation of the immunological system. This theory proposes that the early exposure to a certain and specific group of antigens, not necessarily infectious pathogens, is relevant to teach the human immune system to properly react to the stimuli. In addition, this hypothesis defends that living with anti-hygienic habits do not have an important impact upon the incidence of chronic inflammatory and allergic diseases (Briggs et al., 2016; Rook et al., 2003, 2013; Scudellari, 2017).

Beginning with the simple thought — *being too clean can be harmful to our health* — now the hygiene theory grown and branched into dozens of related variables including the environmental pressure,

microbial exposure, medication, occupation, diet, parasite infection, and others (Bach and Chatenoud, 2012; Briggs et al., 2016; Burrows et al., 2015; Sitcharungsi and Sirivichayakul, 2013; Sorensen and Sakali, 2006; Yazdanbakhsh et al., 2002). However solid, the hygiene hypothesis is far from being perfect or free from opposition. Since the hypothesis creation, many researchers questioned the limited factors. More recently, Bloomfield et al. (2016) said that the term hygiene hypothesis should be abandoned since the authors defend that there is no link between microbial exposure and allergies (Bloomfield et al., 2016), which are still questioned.

### 3. The role of gut microbiome

To complement the hygiene hypothesis, the *microflora hypothesis* comes up with the proposal that, instead of limiting infection, the overall high sanitary standard proposed by the western life-style limits the exposure of people to microbial organisms. Consequently, it modifies the colonization of children's gastrointestinal tract and increases the probability of allergic and autoimmune diseases development due to an immature immune system (Azad et al., 2013; Wold, 1998).

It is known that we carry microbial organisms that make use of our internal structure to survive and multiply, especially our intestine. A vast array of microbes is responsible for occupying all space they can take there. However, we also gain with their presence, as it helps our immune system to mature as well as balance the activity of the immunological pathways (Th1, Th2 and Th17). The immune system presents four major cells patterns of acquire immune response, which are composed by helper T cells (Th) differentiation: Th1, Th2, Th17 and Treg (regulatory T cells). Studies have shown that there are many ways

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