Partnering with the Old Order Mennonites in the Finger Lakes Region of New York State to Identify the Mechanisms of Protective Immunity Against Atopic Disease Development

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Partnering with the Old Order Mennonites in the Finger Lakes Region of New York State to Identify the Mechanisms of Protective Immunity against Atopic Disease Development

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**Abstract:** Old Order Mennonites (OOM) follow a traditional agrarian lifestyle; key aspects include home births, large families, limited antibiotic usage, consumption of whole foods and unpasteurized milk, and early exposure to soil, stables, and farm animals. There is evidence that a farming lifestyle protects against asthma and allergies, yet the biological mechanisms behind this protective effect remain unknown. The “Zooming into Old Order Mennonites” (ZOOM) cohort study was established to further explore protective factors and mechanisms. This study compares immune development among OOM children from the Finger Lakes Region of New York to those residing 65 miles northwest in Rochester, NY. Participants completed prenatal and post-natal questionnaires and biomarker sampling throughout the infant’s first two years. Questionnaires on lifestyle, diet, and environmental exposures continued through year five. The success of this study depended on a partnership between the University of Rochester study team and the OOM community, which began in 2009 with a pilot study on prenatal lifestyle behaviors and environmental exposures. Since then, the study team and the OOM community have collaborated to investigate

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INTRODUCTION

The prevalence of allergic disease, such as eczema, asthma, and/or food allergy, has risen drastically in the past 80 years as society has become more urbanized (Pawankar 2014). It is estimated that around one-fifth of the world’s population is affected by allergic disease, with higher rates among children (Bantz, Zhu, and Zheng 2014). This heightened prevalence appears connected to the rise of urbanization (Moore, Gould and Keary 2003), which points towards an environmental or lifestyle explanation rather than solely a genetic basis. To understand the mechanisms behind the recent rise in rates of allergic disease, it is necessary to study populations whose lifestyle resembles that of an earlier time before urbanization. One such population is the Old Order Mennonites (OOM), who follow a traditional agrarian lifestyle. A long-term partnership has been formed and maintained between researchers at the University of Rochester Medical Center and an OOM community in Penn Yan, Yates County, the Finger Lakes Region of New York State. Using a model of community-based participatory research, we have collaborated with the OOM on several studies to make strides in understanding the decreased prevalence of allergic diseases in farming lifestyle populations.

Penn Yan is a township located 65 miles southeast of Rochester, New York, situated on Keuka Lake in the Finger Lakes region of New York State (Figure 1). Approximately 500 to 600 households of OOMs of Swiss and German heritage reside within this region (Martin 2012b; Martina, et al. 2016; Reid 2015). Their ancestors originally came to Germantown, PA, in 1683 to escape religious persecution and militarism, as the OOM are pacifists (Martina, et al. 2016; Martina, Weiss, and Swan 2012). As the Lancaster County, PA, OOM community grew and the available farmland in the region decreased in size and scope, some Groffdale Conference Mennonites relocated in the 1970s and 1980s to the Finger Lakes Region of New York State and within the surrounding townships of Penn Yan, where they had ample access to farms and farmland (Martin 2012a, 2012b; Reid 2015). Key aspects of the OOM lifestyle include farming as the predominant occupation, exposure to many farm animals, use of horse-drawn carriages rather than automobiles (Figure 2), home births, larger families, consumption of unpasteurized milk, and low rates of antibiotic usage and vaccination (Martin 2012a; Seppo, Choudhury, et al. 2021; Järvinen, et al. 2022).

As a community, the OOM present an opportunity to explore protection against allergy development because of their consistency of cultural practices and lifestyle behaviors. The OOM lifestyle characteristics are markedly different than those of typical Westernized populations; previous studies have suggested an agrarian lifestyle may have protective effects against allergic disease (Braun-Fahrlander, et al. 1999; Kilpeläinen and Koskenvuo 2000). There is a growing body of literature investigating allergic development among other Anabaptist populations, such as the Hutterites, whose members migrated to South Dakota from the South Tyrol in the 19th century, and the Amish, whose members migrated to Pennsylvania, Ohio, and Indiana from Switzerland in the 18th and 19th centuries.
Hutterites, Amish, and OOM populations share many lifestyle traits, including diet, large family size, and farming as the primary occupation. Yet while the Amish and the OOM communities follow a traditional farming lifestyle, the Hutterites operate large, highly industrialized farms, taking advantage of modern technologies. These differences result in decreased exposure to barns and farm animals among Hutterite children, whereas Amish and OOM children have early exposures to these environmental features (Öber, et al. 2017). Furthermore, the rates of allergic disease have previously been compared between Amish communities in Indiana, whose lifestyle more closely resembles the OOM of Penn Yan, and the Hutterites of South Dakota. Approximately seven percent of Amish farm children exhibited allergic sensitization (Holbreich, et al. 2012), compared to one-third of Hutterite farm children (Motika, et al. 2011). Previous research on the Amish and the Hutterites has cross-sectionally focused on the outcome of allergic asthma in school-aged children (Motika, et al. 2011; Stein, et al. 2016; Ober, et al. 2017).

Our goal is to explore early manifestations of allergic diseases in infancy and early childhood, such as atopic dermatitis and food allergy, with a significant focus on identifying the trajectory of microbiome and immune development to identify differences and potential biomarkers of development of or protection against allergic diseases in early life, which provides a potential opportunity for prevention of the allergic diseases. By recruiting mother-infant pairs for a longitudinal birth cohort study, rather than individual children or adults at a cross-sectional time point, we are investigating our hypothesis that both maternal and infant lifestyle play a role in the development of the infant’s immune system and thus risk of allergy development.

**HYPOTHESES: ENVIRONMENTAL AND LIFESTYLE EXPOSURES**

Genetics certainly play a role in the development of the atopic diseases. As an example, multiple studies have pointed to skin barrier function as a potential pathogenesis for atopic dermatitis and food allergy (Yang, Fu, and Zhou 2020). Filaggrin is a key structural protein in the epidermis; genetic variants can result in its loss of function (Yang, et al. 2020; Zheng, et al. 2011) predisposing to barrier dysfunction. Still, genetic differences are unlikely to explain the emergence and rapid increase of allergic atopic diseases world-wide over the past 50 years, highlighting the significant effect of changes in environmental exposures and lifestyle behaviors. While gene-environment interactions may be complex, the suspected role of environmental and lifestyle factors in allergy remains unquestionable.

Over the past 30 years, several hypotheses have emerged to try to explain the dramatic rise of atopic disease. Through an epidemiological study
of British families over two decades long, Strachan (1989) found that children with older siblings were less likely to develop allergic rhinitis and atopic dermatitis. Thus, he proposed the “hygiene hypothesis,” which suggested that “unhygienic” practices, such as exposure to older siblings, increased young children’s exposure to infection, conferred some protection against these allergic outcomes (Strachan 1989). This hypothesis was later expanded to include other lifestyle factors and behaviors representative of recent westernization which may be contributing to the increase in atopic disease (Krämer, Wjst, and Wichmann 1999; Matricardi, et al. 2000). One such expansion, the “old friends hypothesis,” proposed that these living conditions and habits have reduced our exposures to “archaic” microorganisms which would otherwise aid in regulating our immune responses (Rook 2010).

The biodiversity hypothesis, a more recent expansion of the hygiene hypothesis, proposes that the development of atopic disease is closely related to exposure to microorganisms and the subsequent development of the human microbiota (von Hertzen, Hanski, and Haataela 2011; Hanski, et al. 2012). Individuals who are exposed to a greater diversity of microorganisms may have some degree of protection against atopy (Haataela 2019). A child’s diet, mode of birth delivery, exposure to the flora and fauna of farm animals, stables, and interactions within a large nuclear family have been linked to differential rates of allergy (Strachan, 1989; Strachan, Taylor, and Carpenter 1996; Riedler, et al. 2001; Bager, Wohlfahrt, and Westergaard 2008; Abbring, Hols, et al. 2019; Abbring, Ryan, et al. 2019). For example, studies have demonstrated that an infant’s gut microbiome develops differently depending on mode of delivery (Butler, et al. 2020); infants delivered via cesarean birth (“C-section”) are at increased risk of allergic rhinitis and asthma (Bager, et al. 2008). Moreover, consumption of unpasteurized milk has also been linked to differential rates of atopic disease (Braun-Fahrlander and von Mutius 2011). Unpasteurized milk contains bioactive components which may modify one’s immune system and reduce the risk of allergy (Abbring, Hols, et al. 2019; Abbring, Ryan, et al. 2019). These are just a few examples of the many ways in which environmental exposures and lifestyle and behaviors may provide protection against atopic disease development. Therefore, working with the OOM community would offer a meaningful learning opportunity to compare their lifestyle behaviors and environmental exposures to an urbanized population at high risk for the development of atopy in Rochester, NY.

Our work with this community began slowly over many years and with great care toward and respect of the OOM community’s interests in involvement and participation. Our current collaboration with the community was built on three previous studies. What has remained consistent is our respect and inclusion of our OOM partners in the decision-making processes of recruitment, study design, implementation, and dissemination of our research results to the community and discussion of any insights they may have on the outcomes.

CREATING A PARTNERSHIP

The first entry into the Penn Yan OOM community occurred in 2009, for a Center for Disease Control (CDC)-sponsored pilot study on prenatal lifestyle behaviors and environmental exposures. The study collected data through paper surveys as well as lab analysis of urine samples. As the study team sought to assess interest and feasibility of the research, they were mindful of community members’ need for assurance of protecting, and not disrupting, their cultural practices. To meet this goal, community collaboration was a priority from the very beginning. First, over the course of several months, via phone calls and in-person visits, the researcher (CAM) contacted a primary care provider, a nurse-midwife, and OOM community members to identify key OOM informants. The identified individuals were suggested and viewed by their community as more “outward facing” with the English. For example, some had experience speaking to non-OOM audiences about their lifestyle at a local college’s sociology course.

The researcher spoke to the key informants about previous data on the topic of investigation and the research question, and she also inquired about feasibility and potential interest of participation of the OOM community in this study. Upon receiving positive feedback, the researcher and one key informant assembled a focus group to speak further about the proposed study and what it would entail. Since the project would focus on prenatal exposures, attendees of this focus group
were mothers from the community. During this focus group, there was a question-and-answer period as well as designated time to gather recommendations and insights from the attendees on their interest in the study, study design, and recruitment strategies. The focus group informed the study researcher on the best way to approach data collection, as well as who should collect these data. In addition, the researcher shared copies of the lifestyle behavior and household product use surveys which would be used in the study. The researcher wanted to ensure the clarity of questions asked, as well as cultural appropriateness. The OOM women suggested minor changes, and the surveys were revised accordingly. It was also determined by our OOM key informant and focus group members that nurse-midwife (JW) would be the best person to interface with the community during her OOM prenatal visits, as this would be the least disruptive method; she was a well-respected and trusted health provider. Ultimately, 10 participants were enrolled in just one week (Martina, et al. 2012). That study’s results showed significantly lower exposures to endocrine disrupting chemicals (EDCs) amongst the OOM women compared to data from the Center of Disease Control’s National Health and Nutrition Examination Surveys (CDC-NHANES) (Martina, et al. 2012). These chemicals can be ingested, absorbed through the skin, and inhaled via aerosols and nanoparticles (Martina, et al. 2012). They are often found in 1) durable household products and goods, 2) highly processed foods, 3) cosmetics, 4) personal care products, 5) time released pharmaceuticals, as well as in the interiors of motor vehicles (Martina, et al. 2012). The data from the surveys and chemical analysis suggested that OOM lower levels of exposures to these chemicals may be the result of: (1) consuming mostly homegrown produce, (2) no cosmetic use, (3) limited use of personal care products, and (4) their primary mode of transportation other than motor vehicles, such as walking, bicycling and horse and buggy (Martina, et al. 2012).

The second study, conducted from 2013 to 2014, was a survey on the prevalence of allergy and asthma among the OOMs. For this study, we conducted focus group meetings in an OOM key informant’s home to identify the best advertising strategies for recruitment of OOM family survey participation. The group suggested we advertise in the local OOM newsletter The Flame. The OOM community’s enthusiasm for the study was remarkable; when we discussed the benefits of the study, we clarified that the OOM community would not directly benefit but would instead potentially help solve some of the health problems in Rochester. The community was delighted at the prospect of helping others, and so the study began.

After survey distribution and data collection, a new strategy was employed: town hall-style data-sharing meetings. These gatherings were jointly coordinated between the study team and the OOMs; the community recommended locations to maximize attendance. Some meetings were hosted in schools, others in a firehouse, and some at a kitchen table within the community. This cross-sectional survey revealed OOMs do experience significantly less allergic disease and asthma than reported in New York State and by the NHANES (Martina, et al. 2016). For example, the OOM community had a 2.2% prevalence of allergic asthma, compared to the 19% prevalence reported by NHANES (Martina, et al. 2016). A separate survey was mailed to query the community about the prevalence of food allergy, which was not a focus of the prior survey; the survey was followed by a phone call by the study allergist to the families reporting symptoms of food allergy to verify or rule out food allergies (Phillips, et al. 2020). Both adult and pediatric subjects in the community reported 2 to 3 times lower rates of food allergy (confirmed by phone contact) compared to NHANES data (Phillips, et al. 2020). The 30.8% response rate from the OOM may translate to some degree of self-selection for families with suspected allergies (Phillips, et al. 2020), but there are no other large-scale data on the prevalence of allergic disease among the OOM population. However, our recent report on our longitudinal birth cohort study “Zooming into Old Order Mennonites” (ZOOM) confirmed statistically significantly higher rates of atopic dermatitis and food allergy assessed by physician, and food sensitization assessed by specific IgE testing in the Rochester urban population compared to OOM (Järvinen, et al. 2022).

Upon presentation of this data, the community’s curiosity was apparent; attendees were eager to ask questions and propose novel ideas. One person suggested that lower levels of stress and higher levels of community support among the Mennonites might impact their immune system
development, perhaps explaining the lower rates of atopy amongst the OOMs. Data-sharing meetings were a vital part of the research process, as they allowed the OOMs to help shape study objectives. However, the biological mechanisms behind this effect have yet to be fully understood.

MAINTAINING AND EXPANDING THE PARTNERSHIP

A third study collected not only lifestyle behavior surveys and medical history questionnaires but also biomarker samplings, including urine, breast milk, saliva, and feces of mother and infant dyads cross-sectionally in the first year of life and was conducted from 2013-2015 (Seppo, Bu, et al. 2021). Cord blood was collected as a feasibility pilot study towards the end of this study in preparation for a longitudinal birth cohort study which followed. A control arm of 39 Rochester mother-infant pairs was recruited as a comparison. This study required much more care and participation of the OOM community, as we were collecting human samples. In doing so, we presented data from previous studies at town hall meetings (hosted at the Benton, NY Fire Department Hall) and OOM school premises to discuss study results and gather input from the OOM community. We also consulted again with nurse mid-wife JW, who had a large and active practice within the OOM community and was consenting and enrolling interested participants from her practice, as were other birth attendants in the area. Again, we wanted to ensure this study was of interest to the community and feasible for the nurse mid-wife to perform with some assistance from University of Rochester study coordinators. We also needed to ensure we had proper facilities to temporarily package, store, and transport the biomarker samples to our laboratories for analysis. Furthermore, since we were asking more of their time, we again asked for input on the best way to engage the community that was the least disruptive of the community’s cultural practices, and we provided compensation for participants’ time. Ultimately, we recruited 65 OOM participants. From this cross-sectional study, we found evidence that the human milk composition of immune factors, especially IgA antibodies, differs statistically significantly between OOM and Rochester mothers (Seppo, Choudhury, et al. 2021). Additionally, we identified a significant difference in bacterial populations between OOM and Rochester stool samples (Seppo, Bu, et al. 2021).

Together, these previous studies and the established partnership set the stage for an even larger project. With the valued input of the OOM community regarding the previous three studies, we conceptualized and engaged our OOM partners in a five-year study, ZOOM. A longitudinal birth cohort study of mother-infant dyads from the OOM community was enrolled between 2017 and 2020. A comparison group included the suburban/urban community of Rochester families where the infant was at high risk for allergic diseases due to the presence of at least one first-degree blood relative with an allergic disease. Like the pilot study, the ZOOM study protocol involves questionnaires and samples collected prenatally and across the infant’s first two years of life (Järvinen, et al. 2022). This study was funded by the National Institutes of Health and included for the first time a one-time maternal as well as serial infant blood samples at 4 to 6, 12, and 24 months of age, which was initially discussed with a key informant for feasibility (Järvinen, et al. 2022). The study team also collected samples of maternal stool, saliva, nasal, and skin swabs during pregnancy. Once the infant was born, cord blood, stool, and saliva samples, and nasal and skin swabs, from the infant and human milk were collected (Järvinen, et al. 2022).

Study measures reflected questions posed by both our research team and the OOM. For example, a Social Supports and Social Connectedness measure was added as a direct result of the participant who proposed at a data-sharing meeting that OOMs’ decreased stress might be associated with their health outcomes. In this way, the ZOOM study has maintained a model of community-based participatory research. Each child’s allergic status was assessed at study visits, with blood tests for IgE antibodies collected at 1 and 2 years (Järvinen, et al. 2022). This longitudinal birth cohort study certainly requires a higher degree of participant commitment than the previous collaborations with the OOM community, which speaks to the enthusiastic support received from the OOM community. This study required significantly more involvement from the families and the recruitment was performed in collaboration with birth attendants in the community with follow-up sampling performed by a local study coordinator.
Partnering with Old Order Mennonites—Kaplan

who was well known to the OOM community, allowing great participation and retention. We initially recruited about 90 mothers in both arms of the study with a goal of having at least 72 in both arms to complete the study at least through the first year of life. However, enrollment in the Rochester arm had to be increased to 100 mothers because of the high rate of exclusion at birth due to prematurity and illness. We easily attained our goal number of active participants at 12 months of life with this number of initial recruits, and nearly 80 mother-infant pairs in both arms completed the study visits at 12 months.

LESSONS LEARNED

Several successes and challenges have arisen throughout the course of this partnership. One key strategy was the gradual building of new relationships using trusted contacts as “anchor points.” After the pilot study on chemical exposures, a trusted nurse-midwife (JW) and one of the investigators (CAM) jointly introduced the OOM community to a new investigator (JRL) who sought to investigate prevalence of allergy and asthma in the community. Upon completion of that study, the nurse-midwife and these two investigators introduced the community to a third investigator (KMJ), who then began the ZOOM study. Throughout this process, all investigators were mindful of the community’s preferences and lifestyle and reflected carefully on whether each proposed study would respect OOM values. Thus, a strength of this partnership was the slow, thoughtful development of meaningful relationships.

In turn, a challenge has been the disruption of familiarity, or put more simply: change. As with any study, turnover of personnel poses challenges. Participants appeared more at ease when they recognized study team members. To address this observation, a nurse-midwife was present at all study visits and data-sharing gatherings. The COVID-19 pandemic was another significant challenge. While our study team wanted to maintain relationships with our OOM colleagues, we also wanted to promote the safety of the OOM community, knowing COVID-19 vaccination rates may be low among OOM populations. Follow-up visits were paused during March through June of 2020, and some follow-up visits had to be postponed until research activities were resumed in June 2020.

Also, large indoor gatherings to inform the community about the status of the study were paused. However, we continued to contact participants via telephone, letters and cards, and study visits. Through these adaptations, our partnership remained strong throughout the pandemic.

Important lessons have been learned from this collaboration. Respect for the community’s cultural practices has been paramount. This principle can be applied beyond the Old Order Mennonites, to any form of community-based participatory research. Additionally, consistency of research practices, as well as personnel (when possible) can strengthen a partnership with community members. Finally, the importance of data-sharing and community-driven research questions cannot be overstated. The town-hall style data-sharing meetings played a key role in shaping the objectives of the ZOOM study. Without community input, researchers have only a limited view of potential factors. To truly respect a community – especially one who may be considered marginalized and vulnerable due to their religious and cultural beliefs – it is imperative to involve them and collaborate in partnership at every step of the research process.

LOOKING FORWARD

Our ZOOM study team is currently completing 3, 4, and 5-year phone surveys on lifestyle, diet, and environmental exposures, as part of an extension to the original protocol, as well as continuing to analyze the biological samples previously collected from the children’s first two years. The youngest children will soon be turning three years of age, whereas the oldest will soon be six years old. Aligning with findings from previous literature, the rates of allergic sensitization, food allergy, and eczema among one-year-old infants were higher among the Rochester cohort than their OOM counterparts (Järvinen, et al. 2022). Still, there remains far more to understand about the biological explanation for these differences in prevalence rates. We are about to start our fifth study in the community. This includes expansion of the birth cohort and follow-up with the existing subjects at six years of age. We are preparing opportunities and activities to engage the OOM community once again in the upcoming study. The success of this follow-up study will depend on their partnership, and we look forward to gain-
ing their perspectives on our findings thus far and our next steps. Together, we hope to continue to advance our understanding of the complex mechanisms underlying protective immunity against atopic disease.

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