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Review

Design and Progress of Child Health Assessments at Community Support Centers in the Birth and Three-Generation Cohort Study of the Tohoku Medical Megabank Project

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The Tohoku Medical Megabank Project (TMM) has been conducting a birth and three-generation cohort study (the BirThree Cohort Study). We recruited 73,529 pregnant women and their family members for this cohort study, which included 23,143 newborns and 9,459 of their siblings. We designed and are in the process of conducting three-step health assessments for each newborn at approximately ages of 5, 10 and 16. These health assessments are administered at seven community support centers. Trained genome medical research coordinators conduct physical examinations of and collect biological specimens from each participant. The Sendai Children's Health Square has been established as the headquarters for these child health assessments and is utilized to accumulate knowledge that can facilitate the proper practice of child health assessments. We designed all the relevant health assessments facilities to allow parents and their children to participate in the health assessments concomitantly. Our centers serve as places where child participants and their parents can feel at ease as a result of the implementation of safety measures and child hospitality measures. The TMM BirThree Cohort Study is in the process of conducting strategically detailed health assessments and genome analysis, which can facilitate studies concerning the gene-environment interactions relevant to noncommunicable diseases. Through these operations, our study allows for a significant depth of data to be collected in terms of the number of biospecimens under study and the comprehensiveness of both basic and clinical data alongside relevant family information.

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Introduction

The Great East Japan Earthquake and tsunami occurring on 11 March 2011 devastated a wide area of the northeastern coast of Japan. As the middle- and long-term impacts of natural disasters on the health of affected people were a topic of concern, the Tohoku Medical Megabank Project (TMM) (Fuse et al. 2019) was established on 1 February 2012. TMM was operated by Tohoku University (ToMMo) and Iwate Medical University (IMM). ToMMo has been conducting a birth and three-generation cohort study (the BirThree cohort) and a community-based cohort study (Kuriyama et al. 2016). The BirThree cohort study has been recruiting pregnant women, their fetuses (as probands), their partners (fathers of the fetuses), the parents of the women and the partners (grandparents of the fetuses), the siblings of the fetuses (if any) and related extended family members as participants (Ishikuro et al. 2018). Recruitment of pregnant women began in July 2013 and concluded in September 2016, and recruitment of pregnant women and their family members was conducted in obstetric clinics or hospitals by genome medical research coordinators (GMRC) (Kuriyama et al. 2020).

To explore disease-related genes and to clarify the interactions between genetic and environmental factors with respect to noncommunicable diseases, a number of prospective cohort studies have been conducted worldwide (Splansky et al. 2007; Fan et al. 2008; Chen et al. 2011; Long and Fox 2016; Lane et al. 2016). As the study design of prospective cohort studies prevents recall bias and mitigates unnecessary harm or accidents, the many advantages of such studies have been widely recognized. On the other hand, due to the inherent nature of this study design, the prospective cohorts tend to be rather large, often reaching a size of half a million or even one million participants (Collins 2004; Foster and Sharp 2005; Weis et al. 2005; Manolio et al. 2006). We surmised that the use of family information may compensate for a reduction in cohort size; therefore, we planned to conduct a three-generation cohort study. We especially wished to combine a birth cohort with a three-generation cohort (*i.e.*, a BirThree cohort) to study child development extensively in addition to our study of genetic information based on the three-generation family studies. Furthermore, we designed the BirThree cohort as a genome cohort to facilitate genome and omics analyses of the participants.

Among the many important advantages of the BirThree cohort study, we think that the following two are especially important. One advantage is the fact that this cohort study can produce important clues for verifying the developmental origins of health and disease (DOHaD) theory as well as mechanistic insights into this theory (Barker 2007). The other advantage of the prospective birth and three-generation cohort study is that it allows for elaborate analyses of the mechanistic foundation of noncommunicable diseases by its investigation of family members ranging from children to grandparents.

In contrast, the prospective birth and three-generation cohort study is apparently a difficult study, as no large cohort studies of this variety have previously been conducted. The prospective birth and three-generation study, which includes genome analysis, seems to be even more difficult. The prospective birth and three-generation genome cohort study requires well-designed health examination plans for babies, children, mothers, partners, and grandparents as well as well-designed recruiting practices. We have already reported the framework of our BirThree cohort study (Kuriyama et al. 2020). However, health examination of the participants, especially with respect to children born in the ToMMo study (ToMMo kids), is a new endeavor and requires special efforts and design.

The specific purpose of the health assessments of ToMMo kids at approximately the ages of 5, 10 and 16 years is to evaluate their growth and development objectively, which can provide valuable data for future studies in the fields of pediatrics, public health, and pre-emptive medicine. To achieve this purpose, we must conduct health assessments strategically and collect biologic specimens from each participant efficiently. In this paper, we describe the strategy that we established for the baseline examinations of and follow-up for ToMMo kids and their siblings under the age of 20 in our prospective BirThree cohort study, with a particular focus on objective health assessments. As the ToMMo kids were approximately 5 years old during the period 2017 to 2021, we already prepared and conducted health assessments for this age group. Therefore, in this paper, we also report the preliminary progress of this endeavor. We are currently in the process of designing and preparing health examinations of ToMMo kids who will reach the approximate ages of 10 and 16 years in the next five and ten years, respectively.

Study Design and Findings

We have recruited a total of 73,529 participants, including 22,493 pregnant women, 8,823 partners and 8,058 grandparents for the BirThree cohort. A total of 32,602 children, including 23,143 newborns (ToMMo kids) and 9,459 their siblings, were recruited into the TMM BirThree Cohort Study from July 2013 to June 2017 by contacting pregnant women and their family members in obstetric clinics or hospitals when they scheduled their deliveries (Kuriyama et al. 2020). We designed and conducted detailed baseline physical examinations of more than 70% of the child participants and simultaneously collected biologic specimens, including cord blood.

We planned to conduct three health assessments when the children become approximately 5, 10 and 16 years. A flow chart illustrating the design and actual numbers of children who took the health assessments from June 2017 to March 2021 are shown in Fig. 1. As will be described later, we prepared two courses for the baseline assessments: the standard A course and the concise B course (Table 1).

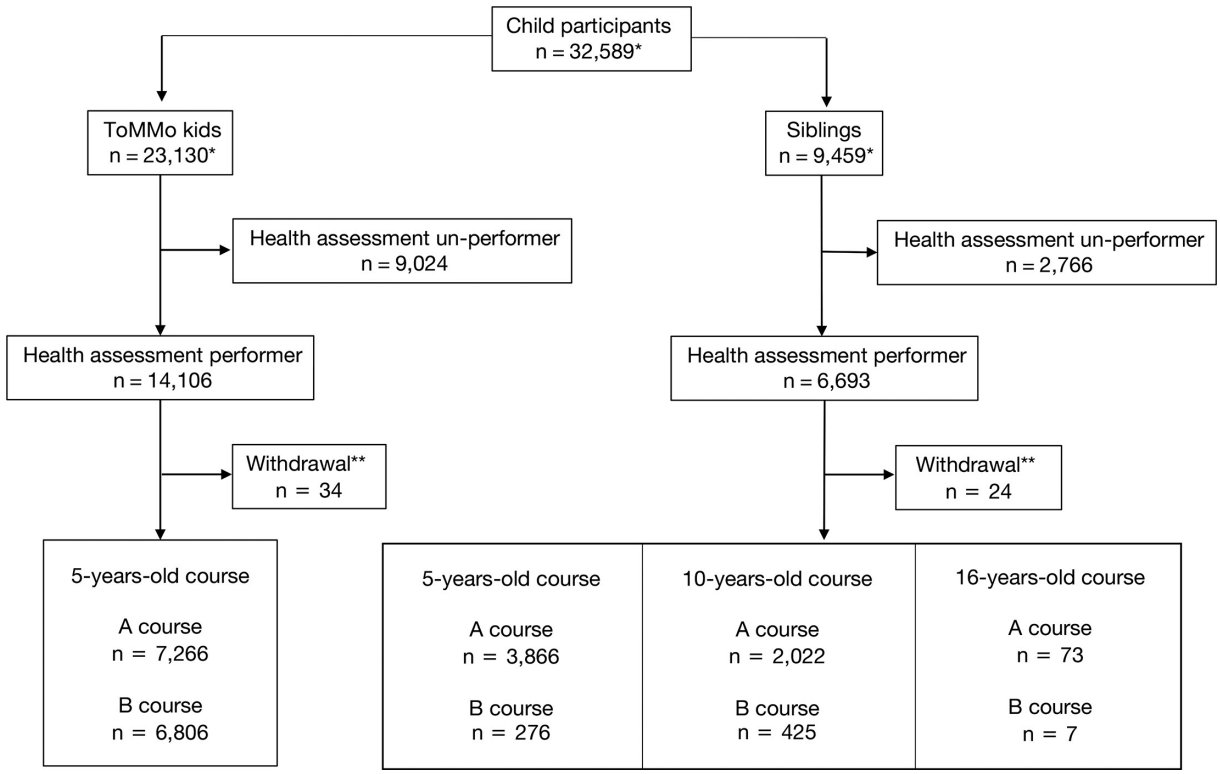

Fig. 1. Flow chart of the number of child participants in each course from June 2017 to March 2021 by age.
*Number of participants according to family role as of 7 October 2020. **Withdrawn from participation as of 9 March 2022.

Table 2 shows the number of data and samples collected from June 2017 to March 2021 following the start of the child health assessments. Details of these efforts will be explained below.

Health examinations of children in the BirThree cohort

1. Data collection for 5-year-old children

Main target diseases of children in the BirThree cohort are mental, allergic, and developmental disorders. Since these disorders are shown to be increased after the earthquake and tsunami, we have been paying special attention (Kuriyama et al. 2016). Biospecimens collected at the community support centers, including blood, saliva, urine, and oral plaque, as well as data collected during the physical and physiological examinations are anonymized and stored in the Biobank. Furthermore, these samples and information are stored in the database of the Tohoku Medical Megabank (dbTMM) for use in future studies (Takai-Igarashi et al. 2017; Minegishi et al. 2019; Ogishima et al. 2021).

Physical and physiological examinations involved in the standard course (the A course) for 5-year-old children consisted of measurements of height, weight, head and waist circumferences, visual acuity, axial length and refraction, an electrocardiogram, a test of hearing acuity, and an oral examination by a dentist. We used standard methodology for these examinations, the details of which are summarized in Table 1. We also conducted analyses using a Gazefinder®, which is an eye-tracking device used for the early detection of autism spectrum disorder in toddlers (Fujioka et al. 2016, 2020; Tsuchiya et al. 2020; Fukushima et al. 2021).

We also collected blood, saliva, urine and oral plaque from the 5-year-old children. These biospecimens were stored in the TMM biobank (Minegishi et al. 2019). The collection of blood samples from 5-year-old children was a difficult endeavor, but we successfully collected 5 ml of blood from approximately 80% of the children. When the blood sample was insufficient or inapplicable, saliva was collected to assure the collection of a sufficient amount of DNA. The blood samples were divided into two groups, one for an allergy test (a total immunoglobulin E (IgE) test, a 39-item allergen-specific IgE antibody test, LSI Medience Corporation, Tokyo, Japan) and the other for DNA extraction. The oral plaque was collected for bacteriological genome examination.

2. Data collection for 10- and 16-year-old children

In addition to the survey items used in the standard course for 5-year-old children, a physical examination course was designed for 10- and 16-year-old children (Table 1). The design of the examination is identical for 10- and 16-year-old participants, and the standard course includes grip strength, casual and home blood pressure, calcaneal ultrasound imaging, body composition, and respiratory function. We collected 10 ml of blood from both 10- and

Table 1. Outline of child health assessments at the community support centers.

		5-year-old standard course (5-year-old A course)	10-year-old standard course (10-year-old A course)	16-year-old standard course (16-year-old A course)	5, 10, 16-year-old simple course (5, 10, 16-year-old B course)
Target age		4-7 years old	8-15 years old	16-19 years old	0-19 years old
Biospecimens	Blood or saliva	DNA extraction			
	Blood test	Immunoglobulin E (IgE) test Allergen-specific IgE 39-item antibody test	Immunoglobulin E (IgE) test Allergen-specific IgE 39-item antibody test Thyroid stimulating hormone (TSH) Free tri-iodothyronine (FT3) Free thyroxine (FT4) High-density lipoprotein cholesterol (HDL-C) Low-density lipoprotein cholesterol (LDL-C) Total cholesterol (T-Cho) Triglycerides (TG) Glycoalbumin (GA) Hemoglobin A1c (HbA1c)		
	Urine	Store at −80 °C			
	Oral plaque	Store at −80 °C			
Physiological measurments	Body measurement	Height Weight Head and waist circumferences	Height Weight Head and waist circumferences Calcaneal ultrasound imaging Body composition		
	Ophthalmology medical examination	Visual acuity Axial Length Refraction			
	Heart check	Electrocardiogram			
	Hearing check	Hearing acuity			
	Oral examination	Check for cavities			
	Developmental test	Gazefinder® (Eye-tracking device)			
	Medical examination		Casual and home blood pressure		
	Lung check		Respiratory function		
	Strength check		Grip strength		
Collection of growth history	Health Status	Copy of participant's maternal and child health handbook			
	Lifestyle of the mothers during pregnancy				
	Birth Information				
	Children's development				
	Immunization				
Incentive	Return the result on the day	Height, weight, head/ waist circumferences, grip strength test, visual acuity/ axial length, blood pressure, hearing test and oral examination			
	Return the result within 3 months	IgE test, allergen-specific IgE 39-item antibody test,TSH, FT3, FT4, HDL-C, LDL-C, T-Cho, TG, GA, and HbA1c Electrocardiogram results of the interpretation by the pediatric cardiologist			

Table 2. Total physiological data and biospecimens collected from child health assessments at the community support centers from June 2017 to March 2021 (a period of 3 years and 9 months)*.

			ToMMo Kids**	Siblings			Total
			5-year-old A and B course	5-year-old A and B course	10-year-old A and B course	16-year-old A and B course	All courses
		Target age	0-7 years old	0-7 years old	8-15 years old	16-19 years old	0-19 years old
Common to all courses	Physiological measurments	Copy of participant's maternal and child	14,239	3,925	2,581	83	20,828
		Weight	7,269	4,058	1,829	72	13,228
		Height	7,267	4,057	1,829	72	13,225
		Waist circumferences	7,260	4,057	1,829	72	13,218
		Head circumferences	7,261	4,058	1,830	72	13,221
		Hearing acuity	6,989	3,975	1,827	72	12,863
		Axial length	7,194	4,033	1,826	72	13,125
		Electrocardiogram	7,127	4,020	1,826	72	13,045
		Gazefinder® (Eye-tracking device)	6,799	2,595	1,087	48	10,529
		Oral examination	7,255	4,049	1,829	72	13,205
		Blood test	5,759	2,939	1,697	71	10,466
	Biospecimens	DNA extraction from blood	5,759	2,939	1,697	71	10,466
		DNA extraction from saliva	2,895	950	332	1	4,178
		DNA extraction from umbilical cord blood	11,225				11,225
		Oral plaque	7,255	4,049	1,829	72	13,205
		Urine	7,081	3,877	1,946	69	12,973
10 and 16-year-old course only	Physiological measurments	Body composition		4,058	1,829	72	5,959
		Calcaneal ultrasound imaging			1,828	72	1,900
		Respiratory function			1,703	62	1,765
		Grip strength			1,823	71	1,894
		Casual blood pressure			1,828	72	1,900
Conducted only at Sendai Child Health Square	Physiological measurments	Home blood pressure			304	9	313
		Visual acuity	2,907	1,916	623	20	5,466
		Refraction	2,925	1,920	623	20	5,488

*Physiological data and biospecimens collected from withdrawn participants are excluded. **ToMMo kids are children born in the ToMMo study.

16-year-old participants. The blood samples were divided into two groups, one of which is used for biochemical examinations examining the following characteristics: 1) thyroid function, including thyroid stimulating hormone (TSH), free tri-iodothyronine (FT3), and free thyroxine (FT4); 2) cholesterol level, including high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (T-Cho), and triglycerides (TG); 3) glucose metabolism, including glycoalbumin (GA) and hemoglobin A1c (HbA1c); and 4) allergies. The other group is used for DNA extraction. The oral plaque was collected for bacteriological examination. Details of the measurement methods and measuring equipment models are as described (Hozawa et al. 2021).

3. Gathering of information concerning the growth history of participants

By copying the Maternal and Child Health Handbook, we obtained objective information related to the health status of child participants from the past to the present. The Maternal and Child Health Handbook has been distributed to all mothers in Japan by municipalities when they become pregnant since 1948. Mothers are requested to keep records concerning their child's health status. Doctors, public health nurses and guardians are also requested to keep records concerning the child's health status, the lifestyle of the mothers during pregnancy, birth information, and the child's development and immunization history in the Handbook (Nakamura 2010).

In addition to the objective health assessments, we conducted a questionnaire survey of child participants and used this survey as objective auxiliary information for understanding their health conditions. Questionnaires are mailed to their parents when the children are 6, 12, 24, 36, 42, 48 and 60 months old. After the participants reach the age of 5 years, we send questionnaires once per year. We also review infants' health examination records by consulting the records of their municipal and school health examinations. In addition, the BirThree cohort study collects information from various sources, including medical records at the time of detection childhood disease indicators, and so on. Details of the survey contents are as described (Kuriyama et al. 2020).

4. Ethics and funding

TMM is supported in part by grants from the Reconstruction Agency, the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and the Japan Agency for Medical Research and Development (AMED). The TMM project was approved by the Ethics Committee of Tohoku University Graduate School of Medicine and the Ethics Committee of Tohoku University Tohoku Medical Megabank Organization. We have conducted the study in accordance with the principles found in the Declaration of Helsinki (World Medical Association 1964), the Ethical Guidelines for Human Genome/Gene Analysis Research (Ministry of Education, Culture, Sports, Science and Technology, Ministry of Health, Labour and Welfare, Ministry of Economy, Trade and Industry 2001) and all other applicable guidelines. We have adopted broad and continuing consent procedures for participants (Kuriyama et al. 2016). For participants younger than 10 years, we obtained informed consent from their guardians. For participants between 10 and 15 years of age, we obtained informed assent from the individuals and informed consent from their guardians. For participants between 16 and 19 years of age, we plan to obtain informed consent from both the individuals and their guardians. For participants with insufficient ability to understand the study protocol at any age, with the approval of the Ethics Committee, we obtained informed consent from their guardians.

Constructing an efficient and integrated health assessments system for child participants

1. Health assessments of children at community support centers

ToMMo established seven community support centers in Miyagi Prefecture (Fig. 2A). We asked the children's guardians to bring the children to nearby centers for health assessments when the children are at the ages of approximately 5, 10 and 16. Trained GMRC are assigned to the community support centers to collect signed informed consent forms and to conduct physical examinations and collect biological specimens from each participant. The licenses of the GMRC have been certified by the Japan Society of Human Genetics and by ToMMo (Sakurai-Yageta et al. 2019). Approximately half of the ToMMo GMRC are qualified nurses or clinical laboratory technicians.

2. Establishment and roles of the Sendai Children's Health Square

At the beginning of the childhood health assessment operation by ToMMo, we planned to accomplish three important missions. First, we wished to construct a system that could allow parents and grandparents to undergo health assessments while their children complete the health assessments, as the TMM BirThree Cohort Study conducts health assessments of parents and grandparents of children concomitant with the health assessments of the children (Kuriyama et al. 2016). Second, we wished to ensure that the health assessments are rigorously secure. Third, children must enjoy health assessments regardless of the presence or absence of their parents. The seven Community Support Centers in collaboration cover all our participants within the Miyagi Prefecture. The number of child participants each center covers are shown in Fig. 2B.

As the Sendai Community Support Center is expected to examine almost half of the child participants, we need to prepare special system. In addition, we felt that in order to accomplish the three missions above, we need to establish a central facility that executes a central role in the provision

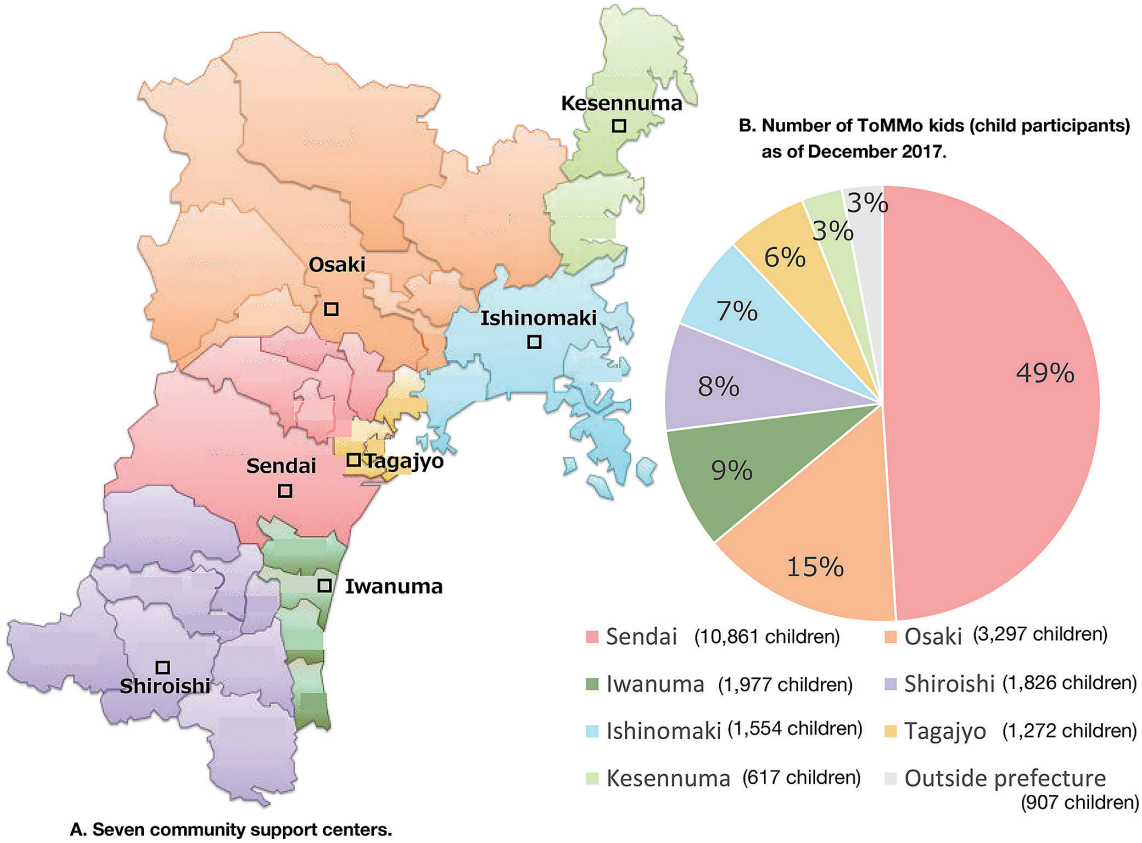

Fig. 2. ToMMo community support centers.
A. Seven community support centers were established in Miyagi Prefecture to provide accurate health examinations of children. B. Number of ToMMo kids (child participants) under the jurisdiction of each of the 7 community support centers as of December 2017.

of childhood health assessments acts as a leader of the other six community support centers in the process of conducting health assessments required specialized, efficient, and reliable operations. To this end, we have established the Sendai Children's Health Square in June 2017 (Fig. 3A). The Health Square has been conducting detailed health assessments of children as a division of the Sendai Community Support Center where parents and grandparents undergo health assessments.

To accomplish the health assessments with rigorously secure, the Sendai Children's Health Square has been working to explore protocols and techniques for the health assessments of children that can ensure safe and elaborate data collection as well as child hospitality. To accomplish enjoyable health assessments of children regardless of the presence or absence of their parents, we are taking care of following child hospitality at the Health Square. First, we equipped a children's room with nursery teachers (Fig. 3A). Second, we introduced many reforms for safety purposes; for instance, the floor of the Square is covered by a carpet so that child participants can sit and walk barefoot. This carpet protects children from suffering damage from falling. We also reduced the number of doors as much as possible so that children are not damaged by doors pinching their fingers. These reforms also make it easier for staff members of the Health Square to track the behavior of child participants. Third, we periodically implement a variety of events (Fig. 3B, C). At these events, children can enjoy the health assessments that are conducted simultaneously.

Thus, the Health Square is playing a pioneering role in incorporating new and innovative health examination protocols and techniques into the ToMMo's child health care assessments. These improvements are incorporated into the routine child health assessment in the other six community support centers.

In addition, the Health Square has been serving as a pilot facility of new approaches for population scale child health assessment. In fact, we challenged two health assessment protocols that are unique to children utilizing the Health Square. From October 2018 to March 2021, we conducted a health assessment that screened for atopic dermatitis with the help of board-certified dermatologists. From October 2019 to August 2020, we conducted a health assessment that screened for neurodevelopmental disorders with the help of board-certified child neurologists.

3. Infectious disease countermeasures at the community support centers

Since February 2020, the infectious disease, coronavirus disease 2019 (COVID-19), has spread in Japan. From

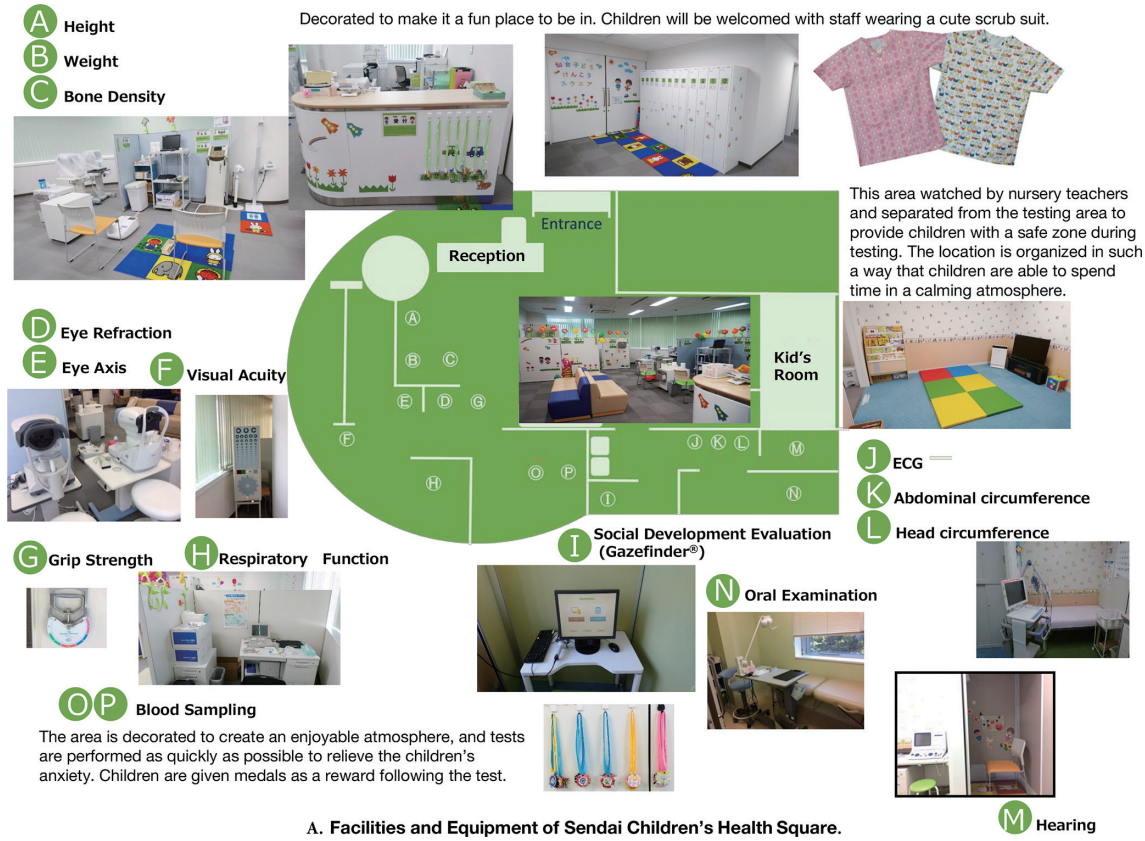

Fig. 3. Sendai Children's Health Square.
A. Sendai Children's Health Square was established in June 2017 as a division of the Sendai Community Support Center due to the fact that a facility involved in the assessments of children's health requires specialized, efficient, and reliable operations. The square is decorated to make it a fun place to visit. Children are welcomed by staff wearing fun and appealing scrubs. This area is watched by nursery teachers and separated from the testing area to provide children with a safe zone during testing. The location is organized in such a way that children are able to spend time in a calming atmosphere. The area is decorated to create an enjoyable atmosphere, and tests are performed as quickly as possible to relieve the children's anxiety. Children are given medals as a reward following the test. B. Sendai Children's Health Square Event 2018. `Great Treasure of Health Assessments Island´ was an event in which child participants could obtain stamps when they completed each health assessments and subsequently exchange the collected stamps for prizes. C. Sendai Children's Health Square Event 2019. `Gather Square Forest´ was an event in which child participants received parts for an animal mask when they completed each health assessments, and if they pasted the received parts onto the mask, the original animal mask would be completed.

March to May 2020, various schools were closed temporarily. Our government instructed children to spend their time at home, so that the community support centers were also forced to close, and the health assessment for the TMM BirThree Cohort Study were suspended for three months.

At the beginning of June 2020, the health assessment was resumed alongside the implementation of extensive preventive measures to prevent infectious diseases. In particular, we designed preventive measures such as *i*) the creation of an elaborate time table for visits to avoid clustering, *ii*) the provision of a mask to all visitors aged 3 and over and asking visitors to wear the masks, *iii*) a screening conducted by doctors to investigate the possibility of infection (pertaining to a health interview, the opportunity to move to an endemic area, and contact history with infected patients), and *iv*) the provision of necessary equipment to GMRC and other staff and a focus on ventilation. Since June 2021, we have established a vaccine injection system for our staff. As a result, we have been able to continue conducting health assessments of children in the centers without spreading infectious diseases.

The use of ingenuity for child participants to complete health assessments

1. *Establishment of a simple course (the B course) in addition to a standard course (the A course)*

The standard course (the A course, Fig. 1 and Table 1) is intended for participants over the age of 4. We assume that it is difficult to implement the A course for participants below the age of 3. When a family visits the center to conduct a health assessment, participants under the age of 3 often come together to the center and spent time with the nursery teacher, while the family was completing the health assessments. In such a situation, participants under the age

B. Sendai Children's Health Square Event 2018. C. Sendai Children's Health Square Event 2019.

of 3 could also contribute to DNA collection and objective health assessments. Therefore, we developed a simple course (B course) that involves an informed consent form for continued participation in this cohort study, a copy of the Maternal and Child Health Handbook, and DNA samples extracted from saliva or cord blood.

In addition, we noticed that some participants might have difficulty visiting the community support centers to contribute to the DNA collection and objective health assessments process. As the B course can be carried out at home, the B course is available to those participants. Another advantage of the B course became clear during the COVID-19 pandemic, during which a considerable number of participants who requested the use of the B course while they were at home.

An important design aspect in this context is that we developed an additional course in which participants who selected and completed the B course are able to visit our community support center at a later date. In this alternative course, which we call the B-to-A course, participants can receive most of the detailed health assessments. The flow chart illustrating the number of child participants in each course by age from June 2017 to March 2021 is shown in Fig. 1. We included the participants who took the detailed health assessments via the B-to-A course as A course participants and excluded them from the list of B course participants in the Fig. 1.

2. *The use of ingenuity to make the community support centers easier to visit*

To make it easier for children and their parents to visit one of the nearest community support centers to complete health assessments, the seven community support centers are regularly open on weekends and during long seasonal school holidays. When we mail an invitation to encourage participants to complete these health assessments, we inform participants of the days when the seven centers are open, mainly including weekends and long holidays, and provide compensation commensurate with their transportation costs.

Ways of increasing motivation to participate in health assessments

1. *Construction of a system to return evaluation values produced by health assessments to participants*

The data obtained via the health assessments are stored in the cohort information management office, and the samples are stored in our biobank super-computer for medical research. We have been encouraging the participants to use their health assessments data to improve their own health. To this end, we are returning the data to the participants alongside standard values. With respect to measured values for height, weight, head/waist circumference, grip strength test, visual acuity/axial length, blood pressure, the hearing test, and the oral examination, our GMRC returned the data

to the participants within a day.

On the other hand, some of the blood samples are sent to a testing company for examinations of the following items (Table 1), which include total immunoglobulin E (IgE) test, the allergen-specific immunoglobulin E (IgE) 39-item antibody test, thyroid stimulating hormone (TSH), free tri-iodothyronine (FT3), free thyroxine (FT4), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (T-Cho), triglycerides (TG), glycoalbumin (GA), and hemoglobin A1c (HbA1c). The results with an interpretation are returned to the participants within 3 months. Electrocardiogram results including an interpretation by a pediatric cardiologist are returned to the participants within 3 months.

If we find critical abnormalities during these examinations, we return the results quickly to the participants and recommend swift consultation with their family doctors via pediatricians working for ToMMo. From June 2017 to March 2021 (*i.e.,* a period of 3 years and 9 months), our pediatrician performed immediate return of the results to approximately 80 child participants.

Physiological measurements and biospecimens collected during the health assessments at the community support centers is stored by the Office of Information Management for the Genome-Cohort Study and Biobank within a day of its collection (Fig. 4).

2. Implementation of a health education event at the centers

Our pediatricians have designed and are conducting a parenting course for parents, taking advantage of the wait time required for their child's health assessments. This course includes lessons concerning how to prevent childhood accidents and basic knowledge pertaining to ways of assessing and supporting the growth and development of children. At Sendai Children's Health Square, the headquarters of child health assessments, we also organize an event to encourage children to become interested in genes and science (https://www.megabank.tohoku.ac.jp/news/16865). This event is also implemented by the other centers.

Discussion

Strengths of the study

The TMM BirThree Cohort Study addresses the importance to conduct follow-up with more than 20,000 child participants and collects not only DNA and blood samples from children and administrative records and questionnaires completed by parents, but also objective health assessments. This depth of data collection, including the number of biospecimens and comprehensive clinical data collected, makes the TMM BirThree Cohort Study quite unique and allows it to serve as a prototypical birth and three-generation cohort study. Several large-scale birth cohort studies are ongoing in Europe, including the Danish

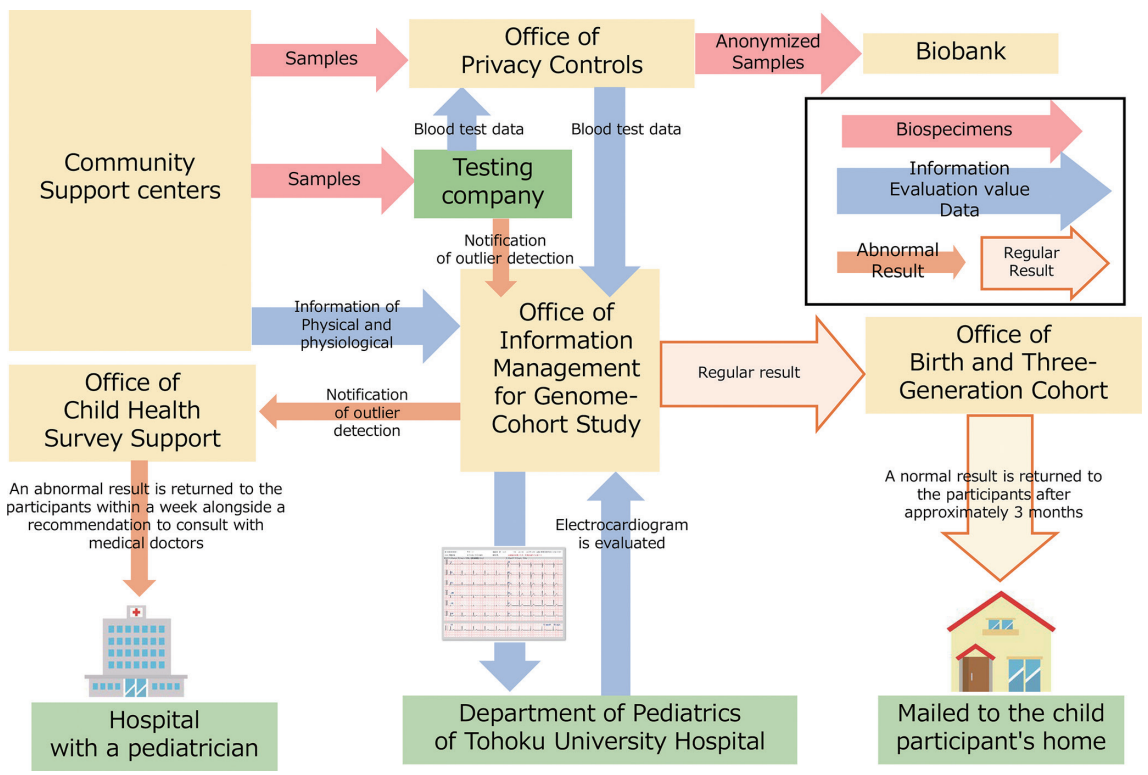

Fig. 4. Flow of information and samples taken from participants at the community support centers.
An abnormal result is returned to the participants within a week alongside a recommendation to consult with their family doctors. Regular results are returned to the participants within approximately 3 months.

National Birth Cohort (Olsen et al. 2001; Andersen and Olsen 2011), the Norwegian Mother and Child Cohort studies (Magnus et al. 2016), the Generation R study (Jaddoe et al. 2006) and the Avon Longitudinal Study of Parents and Children (ALSPAC) (Golding et al. 2001; Boyd et al. 2013, 2019; Fraser et al. 2013). The LifeLines Cohort Study (Stolk et al. 2008; Scholtens et al. 2015) has also been conducting three-generation cohort studies. These cohort studies have recruited more than 10,000 participants and have been expected to harvest important discoveries.

The TMM BirThree Cohort Study tracks child participants by collecting biological samples and information regarding three generations of their families via a questionnaire survey completed by their parents, administrative records, and objective health assessments accomplished through visits to one of seven assessments centers. Despite our desire to ensure deep and elaborate follow-up and assessments, we could find only a limited number of previous examples to guide the design of the objective health assessments by our health assessments centers. Therefore, we have developed an original set of health assessments. In this article, we have discussed how we are establishing a series of objective health assessments and following-up with children. We have designed the objective health assessments by our community support centers, while carrying out reconstruction projects in the areas affected by the earthquake and tsunami. Therefore, in designing the health assessments, we paid special attention to ensuring that the participants could experience peace of mind and enjoyment from visiting the centers as a location for family health management.

ALSPAC is designed to study common disorders, traits and the roles played by common environmental exposures or genetic variations (Golding et al. 2001). The TMM BirThree Cohort Study is a birth and three-generation cohort study that retains similar size to the ALSPAC. We believe that the TMM BirThree Cohort Study, with features of detailed health assessments and large-scale genome analysis, will develop further our understanding of the mechanisms underlying common diseases. We are also hoping to challenge studies concerning relatively rare disorders as well as gene-environment interactions. In fact, from the TMM BirThree Cohort Study, scientific findings have been obtained regarding the relationship between gene and myopia (Fuse et al. 2022), perinatal period psychological stress diseases of mothers and child atopic dermatitis (Kawaguchi et al. 2022), nutritional intake during pregnancy and child development (Yonezawa et al. 2022a, b) hypertension in pregnancy and child development (Ishikuro et al. 2021) etc.

Limitations of the study

In 2016, the TMM BirThree Cohort Study recruited 49.6% of newborns in Miyagi Prefecture (8,605 of 17,347 newborns) (Kuriyama et al. 2020), which counts as comprehensive. However, because of the inherent nature of cohort studies, especially those that include extensive follow-up, we are afraid that this cohort will suffer attrition, which will reduce the power of various analyses. In the TMM BirThree Cohort Study, we recruited approximately 22,000 mothers but fewer than 10,000 partners, and this fact has been limiting extensive trio-based studies. In addition, if we could recruit babies born after the babies involved in the first recruitment, we can challenge quartet-based studies, which have shown extraordinary power in the context of family cohort studies.

In a large-scale cohort, the implementation of detailed objective health assessments for all participants is often difficult. Therefore, it is inevitable that losses will be suffered during follow-up, thus leading to subsequent selection bias, as our cohort study relies on questionnaires and detailed health assessments. In Japan, national health registries are not mandatory, and connections with the registries are not trivial. Therefore, the potential bias introduced by selective participation into the detailed health assessments is a limitation regarding prevalence/incidence measures.

Future research directions

The importance of longitudinal population studies has been recognized unequivocally. The TMM BirThree Cohort Study has addressed the challenges of conducting such a study on a birth and three-generation basis. The study creates research opportunities and benefits researchers by allowing them to access data and biospecimens pertaining to participants' entire life course as well as their family relations. Scientists can incorporate their own research questions into the project on this basis, pending review and approval by our review committee. Examples of current studies include the evaluation of biomarkers in combination with measures of clinical data related to childhood atopic dermatitis and neurodevelopmental disorders. The TMM BirThree Cohort Study is an open longitudinal cohort that will evolve over time to address urgent research needs and contribute to population health.

Conclusion

We describe the strategy and progress of the baseline examinations and follow-up of the ToMMo kids and their siblings under the age of 20 in our prospective BirThree cohort study, with a particular focus on objective health assessments. The TMM BirThree Cohort Study addresses the importance to conduct follow-up with more than 20,000 child participants and collects not only DNA and blood samples from children and administrative records and questionnaires completed by parents, but also objective health assessments. This depth of data collection, including the number of biospecimens and comprehensive clinical data collected, makes the TMM BirThree Cohort Study quite unique and allows this study to serve as a prototypical birth and three-generation cohort study. We believe that prospective birth and three generation cohort study will provide critical information toward the establishment of personalized healthcare.

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Author Contributions

To.K. and Mi.K. have taken responsibility for the entire process of this study and wrote the first draft of the manuscript. N.M., Ma.K., Ta.K., N.F., Sin.K., Sig.K. and M.Y. contributed to the study concept and design. N.M., Ma.K., Ta.O., M.I., C.Y., To.O., K.M., F.U., A.N., A.U., J. S., K.S., E.N.K., Y.H., N.T., M.K., N.N., M.T., M.S.Y., T.T., J.K., M.G., A.O., R.S., H.H., F.N., T.N., A.H., Ta.K., N.F., Sin.K. and Sig.K. contributed to collection of data. S.O. and T.N. contributed to data analysis. N.F., Ta.K. and M.Y. contributed to study interpretation and writing of the manuscript. N.M., Ma.K., R.S., T.N., Sin.K. and Sig.K. provided critical appraisal and contributed substantially to study interpretation and the writing of the manuscript. Sin.K., Sig.K. and M.Y. supervised the study. All authors were involved in writing the paper and had final approval of the submitted and published versions.

Conflict of Interest

The authors declare no conflict of interest.

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