The PROactive Cohort Study: Rationale, Design, and Study Procedures

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Abstract

Children with a chronic condition face more obstacles than their healthy peers, which may impact their physical, social-emotional, and cognitive development. The PROactive cohort study identifies children with a chronic disease at high risk of debilitating fatigue, decreased daily life participation and psychosocial problems, as well as children who are resilient and thrive despite the challenges of growing up with a chronic condition. Both groups will teach us how we can best support children, adolescents and parents to adapt to and manage a disease, as well as tailor interventions to their specific needs.

This cohort follows a continuous longitudinal design. It is based at the Wilhelmina Children's Hospital (WKZ) in the Netherlands and has been running since December 2016. Children with a chronic condition (e.g. cystic fibrosis, juvenile idiopathic arthritis, chronic kidney disease, or congenital heart disease) as well children with medically unexplained fatigue or pain in a broad age range (2-18 years) are included, as well as their parent(s). Data are collected from parents (of children between 2-18 years) and children (8-18 years), as well as data from their electronic health record (EHR). Primary outcome measures are fatigue, daily life participation, and psychosocial well-being, all assessed via patient- and proxy-reported outcome measures. Generic biological/lifestyle, psychological, and social factors were assessed using clinical assessment tools and questionnaires. In the PROactive cohort study the research assessment is an integrated part of clinical care. Children are included when they visit the outpatient clinic and are followed up annually.

Introduction

The PROactive cohort study specifically focuses on three important outcomes for children with a chronic condition: fatigue, daily life participation, and psychosocial well-being. Approximately one in four children in the Netherlands face the challenge of growing up with a chronic condition (a disease which lasts longer than 3 months, recurs more than three times per year, and/or is linked to long-term medication use, treatments, or aid).[1] Children with a chronic condition, such as cystic fibrosis (CF) or juvenile idiopathic arthritis (JIA), face more obstacles than their healthy peers, which impacts their physical, social-emotional, and cognitive development.[2–4] More specifically, 21% of children with a chronic condition report severe fatigue, which affects their quality of life and daily life participation.[5] Because of this, many children experience limitations in their daily activities.[6] Children with a chronic condition reach developmental milestones later than their healthy peers[6]. The challenges encountered are considerably similar across various diseases, pleading for a transdiagnostic approach.[7] Transdiagnostic can be defined as an approach in which clinicians aim to go beyond the disease-specific biological factors of a disease and look for generic factors.[8] It is therefore important to assess fatigue, daily life participation and psychosocial well-being in children with a chronic condition, including different biological, psychological, and social factors that are associated with these generic outcomes in the PROactive cohort study.

The theoretical model behind the PROactive cohort study (Figure 1) is based on the biopsychosocial model, the disability-stress-coping model, and the cognitive behavioral model.[9–11] Figure 1 shows the theoretical models of the PROactive cohort study, 1a displays the biopsychosocial model an 1b gives an overview with elements of all 3 models.

The unique added value of the PROactive cohort study as a child health cohort is that it includes various paediatric chronic conditions that are similarly evaluated. It provides the opportunity to distinguish disease-specific factors from generic, or transdiagnostic, factors. In addition, using the longitudinal design, modifiable risk factors and protective factors, or predictors, can be identified for fatigue, decreased participation in daily life, and decreased well-being in children with chronic conditions across disease group. Another unique added value is the possibility to harmonize and compare outcomes of children with various chronic conditions with healthy peers from the population.[12–14] By harmonizing data collection between PROactive cohort study and population cohort studies we will achieve a better understanding of what challenges are associated with growing up with a chronic disease and what challenges are associated with growing up in today's society, e.g. with the stressors associated with the COVID-19 pandemic. This will help to assess vulnerabilities and resilience among children with chronic and/or life-threatening conditions and their families. This cohort is unique in systematically measuring generic determinants and outcomes across various paediatric chronic diseases and aligning these outcomes with healthy population cohorts.[12, 15–18] Disease-specific cohorts are able to combine patient-reported outcome measures (PROMs) with clinician confirmed biological measurements and variables extracted from electronic health records (EHR), but are often focussed on only one or two different paediatric chronic conditions.[15]

Aim of this cohort

This cohort assesses fatigue, daily life participation, and psychosocial well-being as primary outcomes across children with various chronic condition from childhood to early adulthood. Clinical assessments as well as patient- and proxy-reported biological, psychological, and social factors are used as determinants. We distinguished the determinants as predisposing, direct stressors or mediating factors and considered which of these factors could be a possible treatment target.

Furthermore, the PROactive cohort study identifies children at high risk of debilitating fatigue, decreased daily life participation and psychosocial problems, as well as children who are more resilient and thrive despite the challenges of growing up with a chronic condition. The PROactive cohort study lays a foundation for improving clinical care for children with a chronic disease and their families, and embedded design studies: following children, adolescents and adults with a chronic disease over time in order to monitor them and offer tailored assistance when needed to help them grow up as ‘healthy’ as possible. This knowledge can be used as an innovative and interactive method for creating new group or personalized prevention and treatment strategies. To our knowledge, there are no cohorts that collect data longitudinally, across various paediatric chronic conditions measuring risk and protective factors and outcomes in a similar, transdiagnostic way across diseases in both child and parents.

Study Design

General study design

The PROactive cohort study has a continuous longitudinal design and includes children with a chronic condition in a broad age range. Inclusion can take place between 2 and 18 years of age, depending on the moment of diagnosis. Besides children with a chronic condition, children with unexplained medical symptoms are included in the PROactive cohort study.

Combination research assessments and clinical care assessments within a life cycle perspective

The PROactive cohort study forms an integral part of clinical care. Assessments are directly accessible for health care providers (viewer in EHR) and alerts are noted in the EHR if an individual scores beyond pre-specified thresholds.[19,20] This allows the physician to discuss the results of the questionnaires with the parents and children during an outpatient visit. Fatigue, daily life participation, and psychosocial well-being are assessed using patient-reported outcome measures (PROMs). Previous studies show that discussing PROMs in clinical care can improve the communication between patient and healthcare provider, lead to higher satisfaction with the received care, make problems easier to discuss for patients, and improve clinical outcomes.[21–24] Discussion of PROMs gives health care providers insight into aspects of the child's health and functioning beyond the traditional clinical paradigm.[20,25] It gives children and parents an incentive to participate in the PROactive cohort study. Therefore, the PROactive cohort study does not use waves. Instead, children are included when they visit the outpatient clinic and are followed up annually, preferably linked to another outpatient visit. This interval was chosen, weighing the burden with the possibility to screen for problems and intervene in time. Currently, children are followed until 18 years of age, although follow-up into adulthood is in development.

STUDY POPULATION

Setting

In the PROactive cohort study, participating children complete questionnaires prior to their outpatient visit at the Wilhelmina Children's Hospital (WKZ), the Netherlands. Children with various chronic conditions are included, with different starting points in data collection determined by the debut of their disease: cystic fibrosis (CF; December 2016), autoimmune diseases (such as juvenile idiopathic arthritis (JIA) or systemic autoimmune diseases (March 2017), chronic kidney disease (CKD; June 2019), primary immunodeficiency's (PID; March 2017), inflammatory bowel disease (IBD; March 2019), auto inflammatory conditions (March 2017), congenital heart disease (CHD; July 2019) and children with unexplained symptoms (MUS; March 2017). Neonatology (follow-up of ex-premature) will collaborate at the beginning of 2022.

From 2017 - 2020, children in the first year after treatment for childhood cancer were also assessed as part of this cohort study. At the moment, baseline inclusion in the PROactive cohort study for this patient group has stopped, but follow-up data is still collected in children enrolled in the study until 5 years after

diagnosis in the Princess Máxima Center for paediatric oncology, Utrecht, the Netherlands (collaborating partner).

In- and exclusion criteria

Children with a chronic condition are eligible to take part in the PROactive cohort study, if: 1) they are between 2-18 years of age, 2) they are diagnosed with one of the afore mentioned chronic conditions, and 3) they are at least one year post-diagnosis. Children with unexplained symptoms are included if 1) if they are between 2-18 years of age, and 2) if they present themselves with MUS with pain or fatigue as the main complaint at the Wilhelmina Children's Hospital (WKZ). Children with MUS gives us the opportunity to study our outcomes in children with and without found pathophysiological changes. Exclusion criteria for chronic conditions and MUS symptoms are: 1) not being able to understand or read the Dutch language, 2) not being able to fill out online questionnaires, 3) in case of child-reported questionnaires, cognitive impairment below the level of functioning of an eight-year-old child.

The choice to include children one year post-diagnosis was made for two reasons. First, the diagnostic phase and initial treatment phase are often hectic for parents and children and participation in research, with reflection on psychosocial factors, may be perceived as too burdensome in this phase. Secondly, it may be easier to identify transdiagnostic modifiable or treatable factors when children are in a relatively stable phase of their disease, especially factors that are associated with fatigue.

The lower limit of inclusion from the age of 2 years was determined by the range of the chosen validated questionnaires used.

Informed consent

This study was classified by the Institutional Review Board as exempt from the Medical Research Involving Human Subjects Act (16-707/C). A digital informed consent was provided by both the child (> 11 years) and his/her parent(s) and comprised the use of data from the questionnaires for research and to extract data from the child's medical records

RECRUITMENT AND FOLLOW-UP PROCEDURES

Recruitment

The physician's outpatient clinics are screened to check which children are eligible for baseline assessment. When a child meets the inclusion criteria, the family is invited to fill out questionnaires after obtaining informed consent. For younger children (< 8 years), one of the parents completes the assessment. For older children (8-18 years), both the child and one of the parents are asked to complete the assessment.

For the baseline assessment, families are contacted by e-mail three weeks before a regularly scheduled outpatient visit (Figure 3). Families are contacted twice per e-mail and once per telephone. In case of no

response, this cycle is repeated at their next outpatient clinic visit. After the family completes the assessments, the raw results scores (with traffic light colours), the scores in a chart with threshold and a written summary become visible in the EHR. This makes the questionnaires easily interpretable.

Follow-up

Annual follow-up assessments are linked to an outpatient visit if applicable. Follow-up assessments are divided into core- and extended sets. The core assessment contains a smaller amount of questionnaires focused on the main outcome parameters of the cohort. At the developmentally important ages of 3, 6, 9, 12, 15 and 18 years, children and their parents fill out an extended set of questionnaires (Figure 2). These ages are aligned in a healthy Dutch cohort to allow comparison between chronically ill children and their healthy peers.[12] The current overview of questionnaires of each assessment is available on the PROactive cohort study's DataverseNL page (https://doi.org/10.34894/FXUGHW).[26] For the annual follow-up assessments, families are contacted by e-mail three weeks before a regularly scheduled outpatient visit (figure 3). If no outpatient visit is scheduled they will be contacted 11 months after the baseline assessment. The second follow-up will take place 23-26 months after baseline assessment, the third follow-up will take place 35-38 months after baseline assessment and so on. Children with MUS usually no longer receive hospital care one year after their initial visit. If they are no longer in care, follow-up data is collected only for research purposes.

DATA COLLECTION

Choice of measurements

In this study, we only used validated concepts and (sub)scales that could be compared to outcomes of other studies with healthy children or children with other diseases. Child reported questionnaires are only about the child, parent questionnaires can be both about the child or about the parent themselves. All selected patient-reported biological, psychological, and social factors are related to the primary outcomes: fatigue, daily life participation, and psychosocial well-being. The selection of determinants may also include current topics, such as screen/social media use and the effect of the COVID-19 pandemic on children. All outcomes and determinants of the PROactive cohort study are described in table 1 and 2. Various measurements were aligned with Dutch health population cohorts. [12,14,18]

Data collection PROMs

All PROMs are offered via a web-based portal, KLIK (www.hetklikt.nu). [19,20] Children are allowed to use parental assistance if needed. The estimated time participants need to complete the by PROactive cohort study selected questionnaires is 15-20 minutes for the core set assessment, and 30-45 minutes for the baseline and extended assessment.

Data collection of demographic and clinical data

During outpatient visits several measurements are documented in the EHR. For the PROactive cohort study, we extract data regarding disease activity, disease duration, comorbidities and medication use. Twice a year, data extraction of pre-selected biological variables takes place. If there are several moments of clinical assessments, the data entry closest to filling out the PROMs is chosen.

DATA MANAGEMENT

The PROactive cohort study has a data management plan (DMP) and applies FAIR (Findable, Accessible, Interoperable, Reusable) principles to the data generated in the study [29]. The (re)use of data by internal and external partners to answer more research questions is encouraged. Given the data are sensitive, the data themselves cannot be published openly. However, the metadata are published with a DOI on DataverseNL and will therefore be findable for other researchers (https://doi.org/10.34894/FXUGHW).[26] This metadata includes a data management plan, a description of the data, a codebook, and a Data Access Protocol which outlines procedures and guidelines on how to request and reuse the data. All project materials and data are organized and documented to ensure efficient reuse. The PROactive cohort study attempts to share data in interoperable formats or provide recommendations on how to achieve interoperability. These requests are discussed with clinicians representing the specific disease groups. Depending the nature of the data request, we may either utilize data transfer agreements or the Digital Research Environment (DRE) to share data safely and securely, in line with European data protection and privacy regulations.

CURRENT STATUS

The PROactive cohort study was launched in December 2016. Over time, several disease groups within the Wilhelmina Children's Hospital in The Netherlands have joined. The study is still ongoing and has no expected end date. Inclusions and follow-up assessments are still being collected and the following description is a snapshot of the current status (March 2021). Also, adjustments in collaborating disease groups may change over time.

As of March 2021, N=1918 of the N=2770 invited patients completed the PROactive cohort study baseline and provided informed consent (69% response rate). The PROactive cohort study consist of 1306 child reported baseline assessments and 1761 parent reported baseline assessments. The mean overall age was 11.9 years (IQR: 8.4-15.9 year), 57% of the participants is female. There are seven paediatric disease groups represented in the PROactive cohort study (CF, autoimmune disease, CKD, PID, IBD, CHD, MUS). The overall follow-up percentages across disease groups varied between 54% and 83% (baseline). Figure 4 showes the response rates of the PROactive cohort study.

A cohort specific power calculation[30] was performed, and demonstrated sufficient power with the current inclusions (≥N= 73 advisable). This power calculation is based on 21%[5] expected incidence of fatigue in children with a chronic condition (cross-sectional study), the assumed relative risk of 4, confidence level of 0,95% and the desire power of 80. The data collection system (www.hetklikt.nu) does not allow accidental skipping questions because of this the PROactive cohort study has no missing

values caused by accidental skipping questions. However, it has happened that participants returned questionnaires prematurely, or only the parent version or the child version was completed and not both. Missing data has not been taken into account in the above power calculation.

EMBEDDING

As previously described, the PROactive cohort study consists of a collaboration of different subspecialists in paediatric chronic conditions within the Wilhelmina Children's Hospital Utrecht, the Netherlands. The PROactive cohort study collaborates closely with the Princess Maxima Centre (https://www.prinsesmaximacentrum.nl/en) (paediatric oncology Utrecht, the Netherlands) and Dynamics of Youth[12] (Utrecht University, The Netherlands). There are collaborations with Dutch healthy population cohorts to make it possible to compare children growing up with a chronic condition and healthy children. This concerns the YOUth cohort (Utrecht)[12], HBSC[18] and Whistler Cohort[14]. Since the data collection is still ongoing and growing, the number of collaborating research groups, in- and outside the Netherlands, is expected to increase. The study has an open policy with regard to collaboration with other research groups.

Strengths And Limitations

The unique added value of PROactive cohort study as a child health cohort is that it comprises the data of children with various paediatric chronic conditions who are assessed in a similar way. It provides the ability to distinguish disease-specific factors from generic transdiagnostic factors and it gives the possibility to compare outcomes of chronically ill children to healthy norm populations. In addition, there is a relative high compliance due to the direct applicability in clinical care. Besides assessing patient-reported outcomes, the PROactive cohort study contains biological data from EHR. In the future, the PROactive researchers also aim to collect biobank data (hair and blood).

An important consideration is that PROactive cohort study now aims to include children only after the diagnostic phase. Even so, it may be even better to start measuring children from the moment they receive the diagnosis. Stress linked to the diagnostic process can be a valuable outcome measure for both research and clinical care. Until now we considered this as a burden to children and parents in this hectic time. Nevertheless, the benefit of early screening and intervention possibilities may outweigh the burden. A second consideration is the fact that assessments are not organized in waves but closely aligns with clinical care for the individual patient, Thus, the moment of data collection is adjusted to patients clinic visits. This makes it impossible to work in waves and therefore, exact age and developmental stage differs per child in the cohort. In contrast, working with waves gives clearly defined groups of children with the same age.

Future developments

In the future, we will further professionalize and expand the PROactive cohort study. Professionalization will, for example, evaluation of used questionnaires entail automation of data extraction (both PROMs

and biological data), collecting additional biological materials related to the PROactive outcome measures (e.g. blood and/or hair) for direct analysis and bio banking. A PROactive website is under development. Once available, this will be added to the PROactive DataverseNL page. In the future, an overview of current and ongoing research projects will be made available on the project's DataverseNL page (https://doi.org/10.34894/FXUGHW).

PROactive cohort study aims to stay up-to-date with the latest developments in the field of data collection in children. The Patient-Reported Outcomes Measurement Information System[31] (PROMIS®) is an upcoming development. PROMIS allows for a reduction in the number of questions, which should reduce completion time in the majority of the PROactive patients, while maintaining determinants and outcome measures. The PROactive study team is closely following these developments and aiming to implement them where possible. Currently, children are followed until 18 years of age, although follow-up into adulthood, including transition, is under development.

Declarations

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Non-financial interests: All authors state that there are no professional interests, personal relationships or personal beliefs that may be affected by publication of this manuscript.

Ethics approval and consent

Ethical approval: This study was classified by the Institutional Review Board as exempt from the Medical Research Involving Human Subjects Act (16-707/C and 17-078/C). Informed consent to use the data from the questionnaires and to extract data from the child's medical records was obtained from both the child and his/her parent(s).

Consent for publication: The figures and imagines included in this manuscript are created and commissioned by the PROactive study team. Informed consent was collected through an online portal. Therefore, it is not possible to provide copies of signed consent.

Data availability: PROactive cohort study data contains patient information, which is classified as sensitive data according to European data protection and privacy regulations. For this reason, the data is not openly available and access is only possible through the data request procedure. In order to comply with FAIR principles, the study description, codebook, and the data request procedure is freely available through the following DOI: https://doi.org/10.34894/FXUGHW.[26] For use of PROactive cohort study data is financial contribution requested.

Authors' contributions

All authors meet the following IMCJE authorship criteria: 1) made a significant contribution to the work reported, 2) have drafted or written, or substantially revised or critically reviewed the article, 3) Have agreed on the journal to which the article will be submitted 4) Reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage and 5) agree to take responsibility and be accountable for the contents of the article.

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Tables

Table 1 shows the outcomes and Table 2 shows the determinants of the PROactive cohort study

Outcome*	Primary	Fatigue
		Daily life participation
		Psychosocial well-being
	Secondary	Pain
		Psychosomatic symptoms
		General life satisfaction
**An up to date overview of the used questionnaires can be found at the PROactive DataverseNL webpage[26]*		

Table 2 Determinants within the PROactive cohort study

	Biological	Psychological	Social
Predisposing factors*	Somatic diagnosis Comorbidities Disease duration	Developmental stage High sensitivity	Level of education Social economic status Family composition Family members with a chronic condition
Stressors*	Disease activity Medication use/changes Hospital admission	Psychological effect COVID-19 pandemic Life events	Social effect COVID-19 pandemic
Mediating factors*	Sleep Physical functioning Physical activity	Emotional functioning Pain catastrophizing Anxiety Depressive symptoms Resilience factors Coping Sense of control	Social functioning Social support School pressure Dyadic coping Family empowerment Parental physical functioning Parental psychosocial functioning Screen time/social media use/gaming
**An up to date overview of the used questionnaires can be found at the PROactive cohort study DataverseNLwebpage [26]*			

Figures

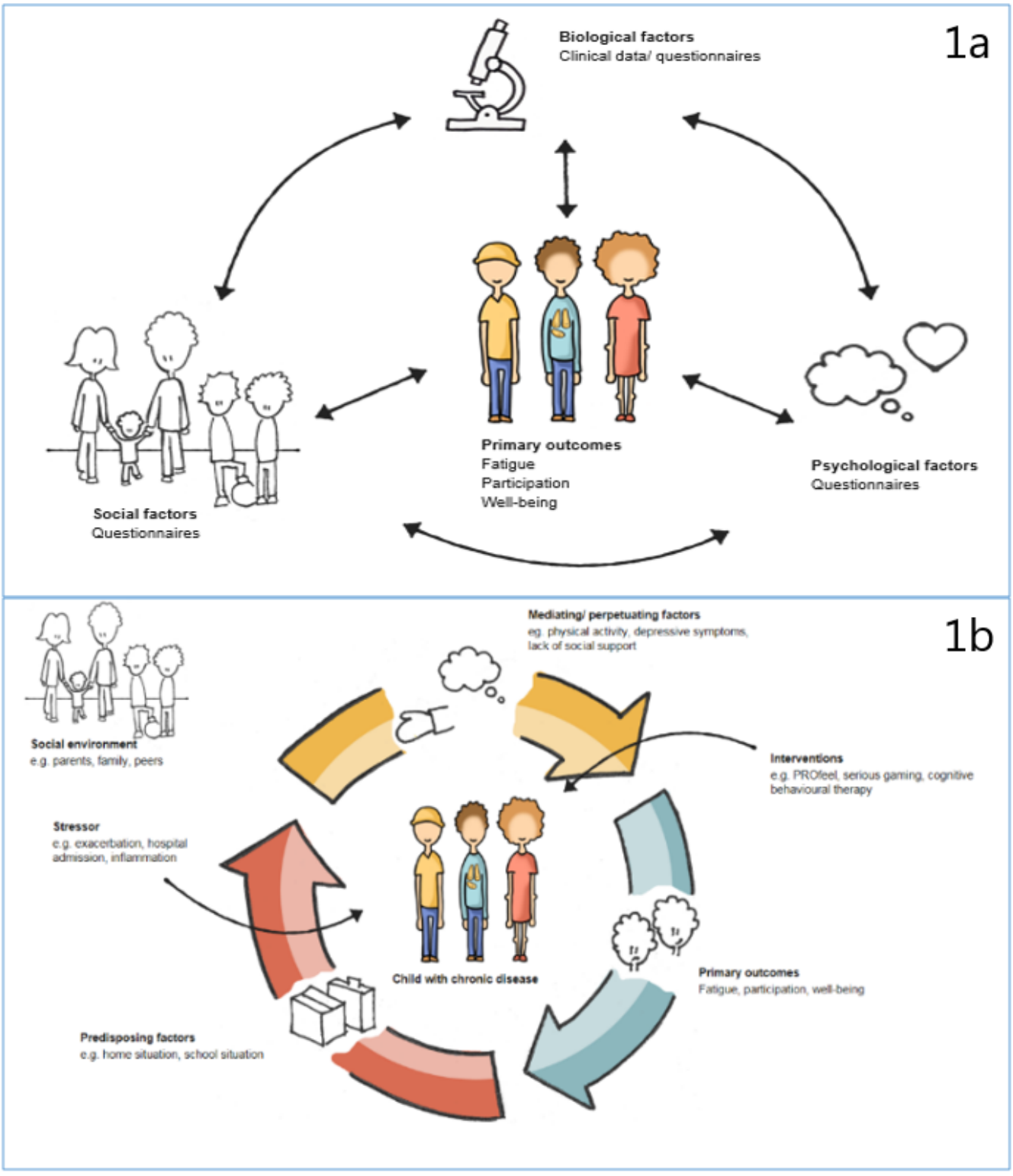

Figure 1

Theoretical model of the PROactive cohort study and the primary outcome measures of the PROactive study. Figure 1a displays the biopsychosocial model; Figure 1b gives an overview with elements of all 3 theoretical models behind the PROactive cohort study (the biopsychosocial model, the disability-stress-coping model, and the cognitive behavioral model.[9–11])

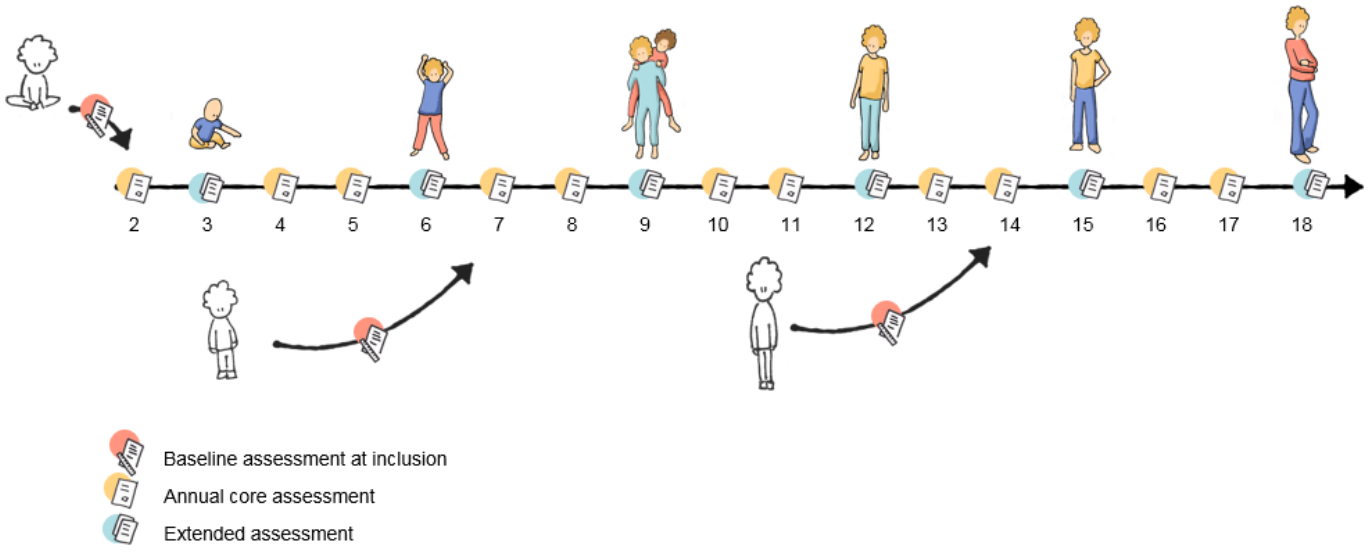

Figure 2

Overview of the annual assessments of the PROactive cohort study

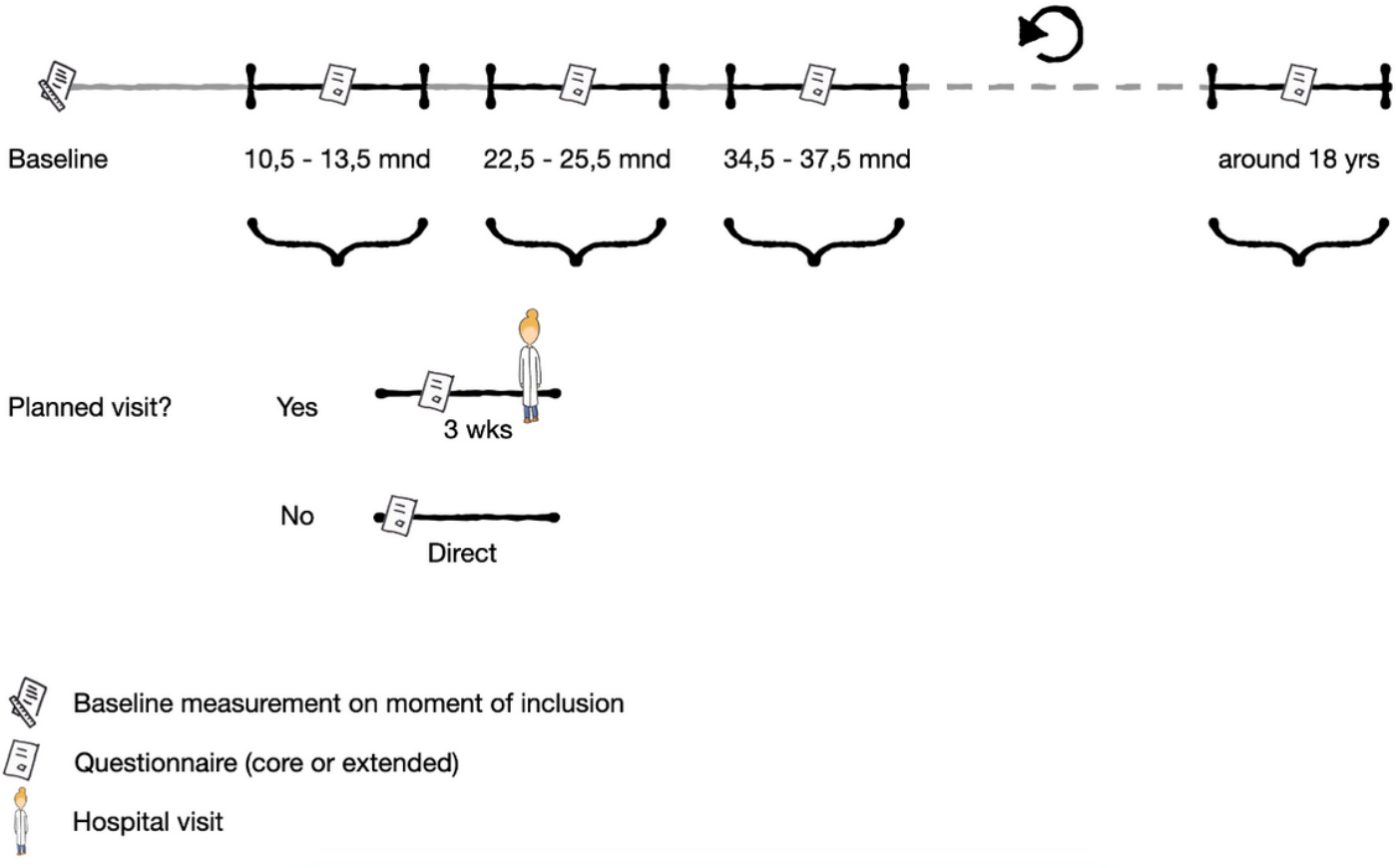

Figure 3

Follow-up approach PROactive cohort study

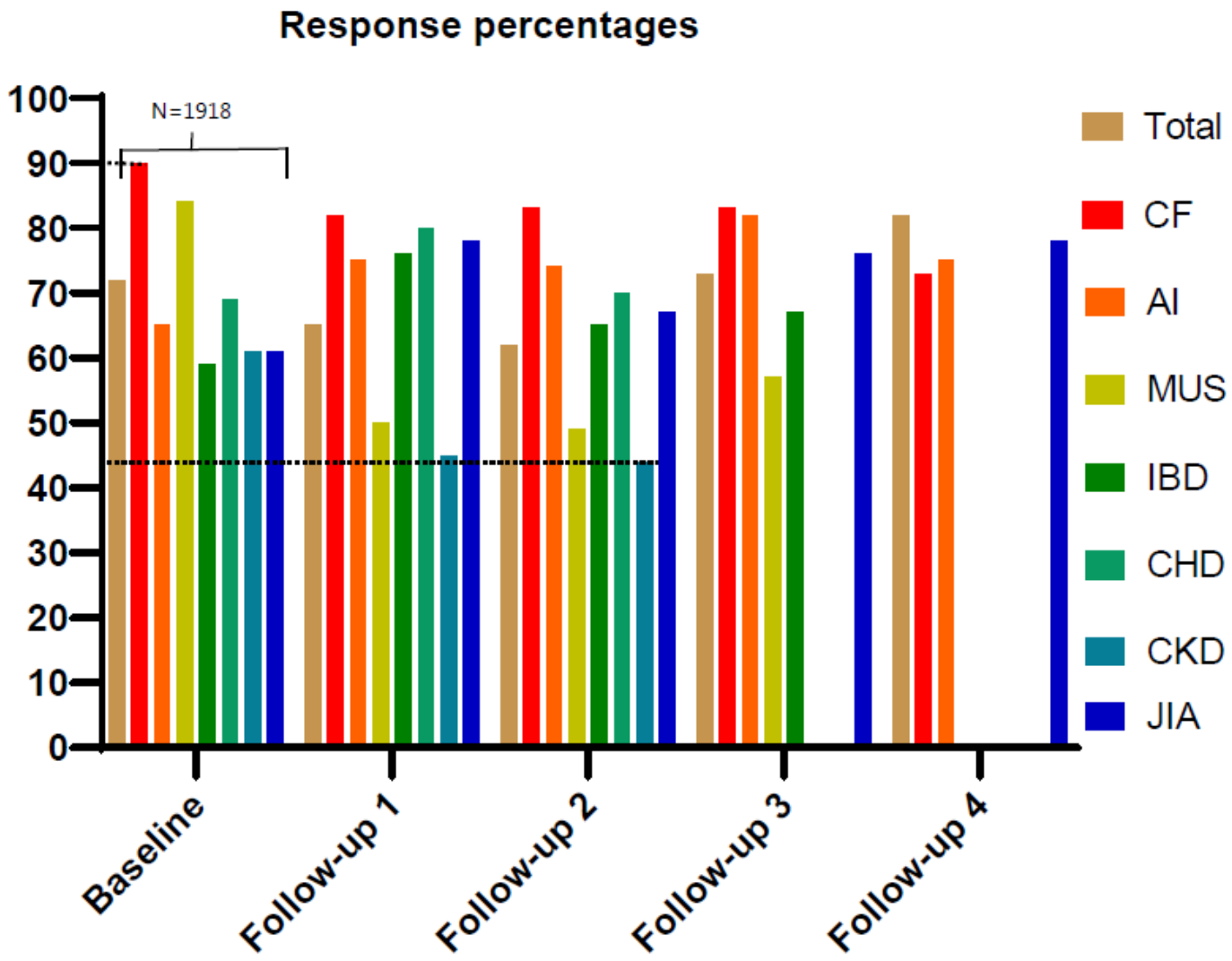

Figure 4

Response rates total PROactive cohort study and across subgroups (Snapshot July 2021) Notes: Response percentages are calculated from patients invited for that specific follow-up moment; The bottom dotted line represents minimum percentages; Top dotted line represents maximum percentages. Abbreviations: Cystic Fibrosis (CF), Juvenile Idiopathic Arthritis (JIA), Autoimmuneconditions (AI; comprises systematic autoimmune diseases, autoinflammatory conditions and primairy immunodeficiencies), Medically unexplained symptoms (MUS), Inflammatory bowel disease (IBD), Congenital heart disease (CHD) and Chronic kidney disease (CKD)