1000 Norms Project: protocol of a cross-sectional study cataloging human variation

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Abstract

Background Clinical decision-making regarding diagnosis and management largely depends on comparison with healthy or 'normal' values. Physiotherapists and researchers therefore need access to robust patient-centred outcome measures and appropriate reference values. However there is a lack of high-quality reference data for many clinical measures. The aim of the 1000 Norms Project is to generate a freely accessible database of musculoskeletal and neurological reference values representative of the healthy population across the lifespan.

Methods/design In 2012 the 1000 Norms Project Consortium defined the concept of 'normal', established a sampling strategy and selected measures based on clinical significance, psychometric properties and the need for reference data. Musculoskeletal and neurological items tapping the constructs of dexterity, balance, ambulation, joint range of motion, strength and power, endurance and motor planning will be collected in this cross-sectional study. Standardised questionnaires will evaluate quality of life, physical activity, and musculoskeletal health. Saliva DNA will be analysed for the ACTN3 genotype ('gene for speed'). A volunteer cohort of 1000 participants aged 3 to 100 years will be recruited according to a set of self-reported health criteria. Descriptive statistics will be generated, creating tables of mean values and standard deviations stratified for age and gender. Quantile regression equations will be used to generate age charts and age-specific centile values.

Discussion This project will be a powerful resource to assist physiotherapists and clinicians across all areas of healthcare to diagnose pathology, track disease progression and evaluate treatment response. This reference dataset will also contribute to the development of robust patient-centred clinical trial outcome measures.

Introduction

Evidenced-based practice is currently focused on patient-centred outcomes [1]. The ability of outcome measures to inform clinical decision-making is dependent on the development of reference values representative of the healthy population. In physiotherapy and other fields of healthcare, an understanding of physical performance and the range of normal variation is essential, as decisions regarding diagnosis, management and prevention of musculoskeletal and neurological disorders are frequently based on comparison with healthy or 'normal' values. To prescribe interventions for improving quality of care, we must first establish a set of clinically relevant measures [2,3]. To evaluate the impact of physical therapies and to communicate clearly and succinctly with colleagues, valid and reliable data are required [4]. At the patient level, a normative reference database provides important information regarding diagnosis, symptom risk and status change in response to

treatment, allowing their progress to be more closely assessed and treatment effectiveness more clearly determined [5]. Greater understanding of physical performance and normal variation in the healthy population and identifying age-related changes in musculoskeletal and neurological function will assist outcome measure development for clinical trials.

Currently limited comprehensive datasets exist detailing the range of normal variation in healthy individuals. Previous studies establishing reference values have typically comprised a limited number of measures and have frequently involved young, disease-free adults, reducing the applicability of the reference data to the wider population [6]. Furthermore, reference values published in restricted access journals can render such data inaccessible to many researchers and most clinicians. Reference value datasets do exist for a select range of measures, such as grip strength [7], range of motion [8], strength [9], and gait [10], however there is no single resource containing reference values for males and females across the lifespan for musculoskeletal and physical performance measures. Therefore, there is an immediate need for reference values that are representative of the healthy normal population and presented in a manner that can be accessed by all [11]. This single resource will be a central point of reference for physiotherapists, clinical researchers and other health professionals to access reference data, including details pertaining to reliability, validity and assessment protocols. The 1000 Norms Project reference dataset will stimulate high impact research activity, enabling robust evaluations with sensitive outcome measures, analysis of clinically relevant subgroups and a greater understanding of the interactions and associations between different musculoskeletal and neurological measures of health. The need for standardised measures has also been identified by the National Institutes of Health (NIH) who developed the NIH Toolbox to advocate for standard assessment of neurological and behavioural function [12]. The NIH Toolbox is a set of standard measures within the domains of cognition, motor function, sensory function and emotional health. The 1000 Norms Project will contribute to this international focus on accurate outcomes by producing a large reference dataset of standardised musculoskeletal and neurological measures collected in a cohort of healthy individuals across the lifespan.

Research focusing on ageing and lifestyle has demonstrated that habitual physical activity interacts with ageing and has the capacity to modulate musculoskeletal health and functional performance [13]. The influence of epigenetic factors, notably physical activity habits on muscle phenotypes in the elderly, suggests that genotype is possibly the strongest candidate to explain variance among muscle phenotypes [14]. Alpha-actinin-3 (ACTN3) has been identified as one of many genes contributing to genetic variation in muscle performance and adaptation to exercise. ACTN3 has been shown to have a beneficial effect on the function of skeletal muscle in generating muscle force [15,16]. Several cross-sectional studies indicate an association between athletic performance and ACTN3 genotype [16–18], however participants in these studies were highly trained athletes and may not be representative of the general population. Hagberg et al. [19] states that whilst there is evidence that ACTN3 acts as a contributor to muscle trait variation, the importance in the untrained population remains unclear. Further studies are needed to establish the influence of ACTN3 on functional abilities in elderly populations, for instance, to target individuals who may be more susceptible to the effects of sarcopenia and require specific interventions [20,21]. The 1000 Norms Project will contribute to the understanding of the genetic contribution to human phenotype by investigating the association of ACTN3 genotype with the physical performance items related to strength and power in individuals across the lifespan.

The primary aim of the 1000 Norms Project is to generate a wide ranging database of musculoskeletal and neurological reference values in a cohort of 1000 healthy individuals aged 3 to

100 years. A secondary aim is to develop predictive equations adjusted for factors such as age and gender for each individual measure.

Methods

Overview of the study design

In 2012, the 1000 Norms Project Consortium, an interdisciplinary multi-institutional collaboration of researchers, clinicians and higher degree students, designed the 1000 Norms Project over a four stage process which included: (1) the establishment of working parties, (2) a comprehensive review of the definition of 'normal', (3) identifying viable sampling and recruitment strategies, and (4) selection of clinically relevant patient-centred musculoskeletal and neurological items to be collected in the Project. Expert physiotherapists, scientists and clinical researchers were invited to join the 1000 Norms Project Consortium to contribute or recommend items for inclusion in the Project. Items were considered for inclusion if there was an absence of high quality reference data across the lifespan, if they had acceptable psychometric properties and were feasible in terms of time and equipment. Items had to be measurable across all ages, with low ceiling and floor effects, and had minimal risk of injury to participants and examiners. For the selection criteria of items considered for inclusion in the 1000 Norms Project, see online supplementary Appendix A. A flow chart summarising the selection process is shown in Fig. 1. Items aligned with current research foci, such as the performance based tests recommended by the Osteoarthritis Research Society International (OARSI) [22] and the NIH Motor Assessment [23] were also considered.

Potential items
- Physical profile (10)
- Ambulation (9)
- Balance (3)
- Dexterity (2)
- Endurance (3)
- Joint range of motion (21)
- Motor planning (2)
- Strength (23)

(n= 73)

Reliability and validity *not* well established
(n=9)

Potential items with acceptable psychometric properties
(n=64)

Items deemed infeasible
(n=8)

Reliable and feasible items
(n=56)

Not measurable or safe to perform across the lifespan
(n=4)

Reliable, feasible, safe and measurable items across the lifespan
(n=52)

Item already represented within the construct
(n=5)

Reliable, feasible, safe, measurable item across the lifespan that represents the construct
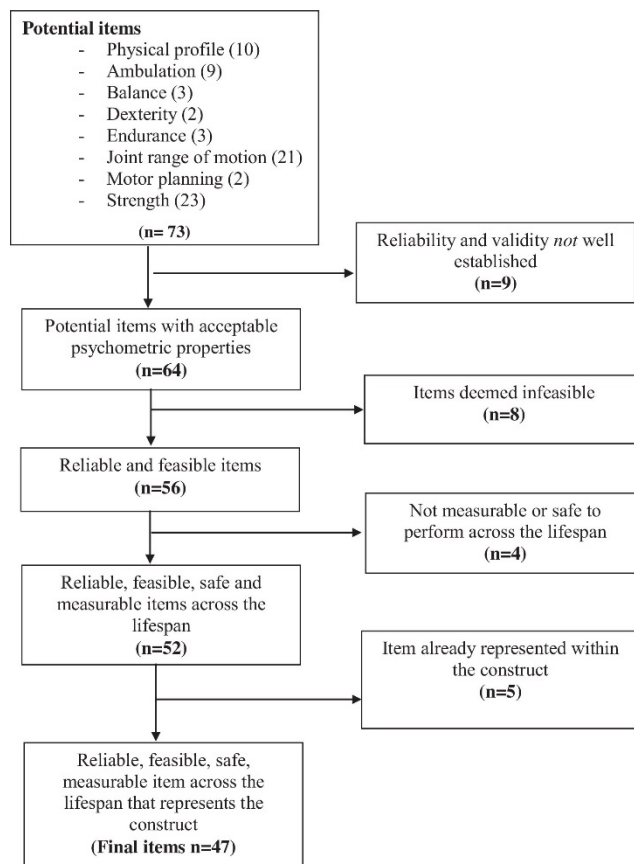**(Final items n=47)**

Fig 1.

The 1000 Norms Project is a cross-sectional study which has received institutional ethics approval. The descriptive nature of the 1000 Norms Project as well as the number and age range of

participants makes it ideally suited to a cross-sectional study design. There is no loss to follow up and this design allows researchers to investigate associations between a wide range of outcome variables. Participants will also be invited to express their interest in participating in future research involving the 1000 Norms Project, creating the possibility of a longitudinal cohort investigation. Consent will be obtained from all participants aged 18 years and over, and from a parent or guardian for all participants aged between 3 and 17 years. Separate consent will be obtained for the collection of saliva DNA.

Recruitment strategies

The 1000 Norms Project Consortium endeavoured to identify a sample of individuals living in Australia who are representative of the healthy 'normal' population across the lifespan. Previous studies involving large reference cohorts were evaluated for recruitment strategies, sampling methods, response rates and feasibility [8,24–26]. Stratified random sampling options were extensively investigated such as accessing the electoral roll and Medicare government databases. In Australia, sampling and recruitment strategies have altered greatly with the implementation of the Privacy Act 1988 and its associated amendment, the Privacy Amendment (Enhancing Primary Protection) Act 2012, the Personal Information Protection Act 1998 (NSW) and the Health Records and Information Privacy Act 2002 (NSW), preventing access to role based data for research purposes. The possibility of employing external companies to randomly contact individuals and screening for participation in the 1000 Norms Project was also explored. However, the Australia Communications and Media Authority states that the 'mobile phone only' population in Australia in 2012 was 20%, rendering a truly random sample via landline contact less likely. As such, the 1000 Norms Project Consortium concluded that a highly structured convenience sampling strategy would be used.

Local recruitment of participants in the Sydney metropolitan area surrounding the Faculty of Health Sciences, The University of Sydney Lidcombe, New South Wales, Australia, will be targeted since it demonstrates similar socioeconomic representation of the greater Australian population according to the ABS Socio-Economic Indexes For Areas (SEIFA) [27]. Information regarding ethnicity and socioeconomic status, including levels of education and occupation, will be collected to further define the representativeness of the sample for external validity. Utilising a variety of advertising mediums, initial contact will be made with potential participants via: council, community and religious groups, aged care independent living facilities, public and private schools, government subsidised and private childcare centres, sporting clubs, local area housing and shopping centres, social media (Facebook and Twitter), as well as tertiary and vocational education institutions. A variety of print, radio and television media will also be conducted. The recruitment and advertising campaign will be delivered in promotional waves every two months until data collection is complete.

Potential participants will be invited to contact the 1000 Norms Project coordinators (M.J.M. and J.N.B) for a telephone interview to assess eligibility and schedule an appointment for assessment. Eligible participants will be sent a detailed information package and a confirmation phone call two days prior to their appointment. All non-attendances will be contacted twice to reschedule.

Table 1 Age distribution of participants.

Age Group (year)	Number of participants
3 to 9	140 (20 per age year)
10 to 19	160 (16 per age year)
20 to 29	100
30 to 39	100
40 to 49	100
50 to 59	100
60 to 69	100
70 to 79	100
80 to 100	100

The highly structured convenient sampling approach was devised by the 1000 Norms Project Consortium as it was the most feasible and efficient way to recruit participants given the nature of the study (i.e. large scale, participants across the lifespan, location of the study). The extensive range of recruitment techniques utilised to enlist potential participants from diverse socioeconomic and cultural backgrounds, as well as people from a broad range of physical fitness and sport involvement will minimise potential sources of sampling bias [28] and volunteer bias [29]. Information bias [30], which includes systematic distortions or errors when collecting and measuring an outcome, has been dealt with through careful planning and study design, including rigorous training, piloting and reliability testing prior to commencement.

Participants

The 1000 Norms Project will recruit 1000 participants aged 3 to 100 years. Age will be based on the last birthday. Equal numbers of males and females will be recruited to represent the Australian population and participants will be stratified for age as shown in Table 1. Oversampling of participants in the younger age groups (3 to 19 years) has been planned to reflect the rapid changes associated with maturation and growth during this period.

To ensure a cohort representative of the healthy 'normal' population, a set of self-assessment inclusion criteria to classify health status have been determined according to the World Health Organisation [31] and Rattan [32] (definitions). The 1000 Norms Project defines health as a state of adequate independence in daily life and describes the ability of individuals to adapt to the expected occurrence of sickness and disease.

Potential participants will be asked the following questions:

1.

"Do you consider yourself healthy for your age?"

2.

"Are you able to participate in normal activities of daily life with respect to your age?"

Individuals who respond affirmatively to both questions will be considered potential participants, and screened for any of the following exclusion criteria:

1.

Inability to follow age-appropriate instructions during the physical assessment

2.

Insufficient English to complete questionnaires

3.

Self-reported health conditions or factors affecting physical performance

4.

Presence of the following conditions: diabetes mellitus; malignant cancers; demyelinating, inflammatory and degenerative neurological conditions; pregnancy; class 3 obesity (BMI >40); severe cardiac or pulmonary disease affecting performance of daily activities; history of major surgery affecting physical performance; infectious or inflammatory arthropathies; severe mobility impairment necessitating dependence on mobility aids for all ambulation (outdoor or occasional use permitted)

Due to the physical nature of most measures, the inclusion/exclusion criteria do not categorically exclude participants who may have mental health, cognitive or behavioural dysfunction. If potential participants report that they consider themselves healthy for their age and are able to participate in activities appropriate for their age they are then reviewed for the exclusion criteria.

The inclusion/exclusion criteria and sampling strategy increases generalisability (external validity) of the Project, especially to populations considering themselves healthy for their age and will be relevant to multicultural/multinational populations similar to Sydney, Australia. The exclusion of conditions associated with altered physiological characteristics or abnormal function is necessary to ensure the sample reflects an appropriate level of health. The selection criteria will generate a reference sample that is representative of the healthy population and therefore generalisable to individuals who participate meaningfully in everyday life [32]. It is also necessary to ensure that the sample does not include only disease-free individuals, as disease and sickness are an expected experience of the normal ageing process.

Generalisability (external validity) will be assessed in two ways:

1.

Collecting participant details related to ethnicity such as country of birth and family heritage to compare to other cities and countries.

2.

The Socio-Economic Indexes For Areas (SEIFA) indexes, a widely used measure of relative socio-economic status of different postcode areas, providing contextual information about the area in which a person lives."

Procedure and setting

Participants will attend a single appointment for assessment of physical measures, completion of questionnaires and collection of saliva DNA. The 1000 Norms Project Protocol Booklet, a comprehensive resource describing each item measured in the Project, will be used to ensure consistency throughout the data collection process (online supplementary Appendix B). The standardised procedures, verbal instructions, and scoring systems are provided for each item. Items have been divided into two categories: physical profile and physical performance. Physical profile relates to anthropometric and structural features, while physical performance examines the ability to carry out physical tasks. Assessments of physical performance are further categorised into seven constructs: dexterity, balance, ambulation, range of motion, strength and power, endurance, and motor planning. The individual items to be included in each of these constructs were identified by the 1000 Norms Project Consortium as those of most interest, and demonstrated sufficient reliability and construct validity to represent the construct being examined (Table 2).

All assessments will be conducted by experienced physiotherapists, either M.J.M. or J.N.B., in the Sydney Performance Laboratory, Faculty of Health Sciences, The University of Sydney. Each item will be performed in a standardised order to ensure consistency for comparative data analysis. Participants will be given short breaks throughout the assessment according to their individual needs. All items are intended to be completed by all participants in two to three hours and are not anticipated to cause physical discomfort. Participants may choose not to undertake any of the items, and if a particular item is judged to be beyond the capability of the participant it will not be attempted and no score will be recorded. Safety considerations have been incorporated into the protocol for each item. A pilot study of 10 participants to evaluate feasibility and reliability of the protocol was conducted in September 2013 and demonstrated excellent inter-rater reliability (interclass correlation coefficients >0.75) between the two examiners (M.J.M. and J.N.B) for all measures.

Demographic details as well as self-reported validated measures of quality of life, lifestyle, levels of physical activity, work capacity, pain and knee/ankle health will be collected. Questionnaires and the details of the age groups to which they are administered are outlined in Table 3. Individual saliva DNA Kits (Norgen Biotek, Thorold, ON, Canada) will be used to collect a 2 mL saliva sample according to the manufacturer's protocol. General infection control precautions and standardised procedures will be followed during saliva collection.

Data processing and statistical analysis

Descriptive statistics will be applied to the data, creating mean values and z scores in SPSS v22 (IBM SPSS Statistics for Windows, Armonk, NY, USA). Comprehensive tables of mean values and standard deviations stratified by age and gender will be generated. A sample size of 1000 will provide precise estimates of normal values for age and gender groups with narrow 95% confidence intervals. Age-specific centile charts will be developed using quantile regression analyses and 95% confidence intervals will be calculated about these quantiles. Correlation analyses will be used to identify

univariate associations between items and multiple regression analyses will be used to generate predictive equations adjusted for age and gender.

Missing data will not be imputed. The 1000 Norms Project has been prospectively designed to minimise missing data through careful data collection methods and rigorous data cross-checking. Whilst there is no universally accepted statistical method to cope with missing data, all missing data will be described to allow readers to judge the validity of the findings [33].

The de-identified 1000 Norms Project dataset will be released to the international community by March 2016 in a freely accessible, practical and publicly accessible format by Intersect Australia Limited, a not-for-profit company providing eResearch data storage (www.intersect.org.au).

Discussion

Knowledge of normal variation of healthy individuals is essential to identify deviation from normal and to evaluate responses to physiotherapy and other treatments. Through improving our understanding of the normal range of healthy variation, the 1000 Norms Project will assist outcome measure development and greatly contribute to future patient-centred outcomes research. Whilst some normative reference values exist, there is a lack of comprehensive data cataloguing the physical performance and functional ability of healthy individuals across the entire lifespan. This project will establish a freely accessible reference dataset of over 50 musculoskeletal and neurological measures of a healthy population aged 3 to 100 years. Data from the 1000 Norms Project will assist future studies in physiotherapy to more accurately define normal (and abnormal), and develop norm-referenced outcome measures in clinical trials and studies of natural disease progression. Management of chronic musculoskeletal diseases such osteoarthritis depends on identification of physical impairments in strength, joint movement and balance, and resulting activity limitations such as walking and stair-climbing. The 1000 Norms Project reference database will provide 'normal' values for these outcomes, greatly assisting in the diagnosis of physical impairments and guiding best-practice management and evaluation of treatment interventions.

Research investigating the relationship between genetic variation and physical characteristics in healthy populations is limited. The 1000 Genomes Project involved the mapping of genetic variation from different genomes and provided insight into the degree of normal genetic variation that exists between healthy individuals [34]. The 1000 Norms Project will contribute to deep phenotyping musculoskeletal and neurological conditions and the influence of genotype on physical performance through the analysis of power and speed measures in participants who have been tested for the ACTN3 gene. Investigating the relationship between ACTN3 genotype and physical performance measures in healthy norms will increase our understanding of how this polymorphism might have an effect on muscle function and influence therapies to improve healthy ageing.

The 1000 Norms Project will generate new information for the age-appropriate capabilities of healthy 'normal' individuals. This information is intended to aid all healthcare stakeholders: researchers, physiotherapists and allied health clinicians, caregivers facing health care decisions and health policymakers considering the value of interventions and disability supports and services. The 1000 Norms Project will improve our understanding of normal variation and assist clinicians to diagnose pathology, track disease progression and evaluate response to treatment. The resulting database will contribute to the development and validation of age- and gender-relevant clinical trial outcome measures. The 1000 Norms Project Database will provide a unique collection of healthy

normative measures to further understand musculoskeletal and neurological dysfunction and age-related pathological changes.

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