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The Impact of a 6-Week Physical Activity Intervention on the Aerobic Capacity, Quality of Life, and Physical Activity Levels in Patients with a Chronic Disease.

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The impact of a 6-week physical activity intervention on the aerobic capacity, quality of life, and physical activity levels in patients with chronic disease.

Abstract

Introduction: Maintaining a physically active life is crucial for people with chronic diseases. It provides many health benefits and can slow or even prevent disease progression. The aims of this evaluation were to determine whether changes existed in aerobic capacity (AC), quality of life (QoL), and physical activity (PA) levels after a PA intervention, and if these were sustained long-term. It also sought to determine which diagnosis groups incurred the greatest benefits.
Methods: A 6-week PA intervention was conducted. Patients completed tests for AC (VO_2 and six-minute walk), QoL (SF-36 questionnaire), and PA levels (R&G questionnaire) at baseline, immediately post-intervention, 6-months post-intervention, and 12-months post-intervention.
Results: Currently, 383 patients are enrolled and comprise 6 different diagnosis categories (Cancer, HIV/AIDS, cardio-metabolic, respiratory, neuromuscular, and mental disorders). Those with respiratory disease commenced the intervention with the lowest AC, whilst those with mental disorders had the lowest baseline QoL. The PA levels at the beginning of the intervention were remarkably low (67% inactive) and did not differ by diagnosis group. For the 275 patients who have completed the intervention, a significant ($p<0.05$) change was determined for all outcomes. Those with mental disorders had the largest increase in their QoL scores and those with cancer had the largest change in PA levels. Only 34% of patients were classified as inactive immediately post-intervention; which was sustained at 12-months post intervention. The initial increase in VO_2 (+10%) was no longer significant after 12-months, but a lasting change was seen in the 6-minute walk test. Physical QoL remained elevated, and was largely explained by PA levels, while mental QoL returned to baseline.
Conclusion: A 6-week PA intervention can induce long-term changes in PA levels and AC in a broad range of chronic disease patients. The increased levels of PA in turn can lead to increased physical QoL.

Key Words: physical activity; chronic disease; quality of life; aerobic capacity; exercise intervention

L'impact d'une intervention de six semaines d'activité physique sur la capacité aérobie, les niveaux d'activité physique et la qualité de vie de patients atteints de maladies chroniques

Résumé

Introduction : Le maintien d'une vie physiquement active est crucial pour les personnes atteintes de maladies chroniques. Cela procure de nombreux bienfaits pour la santé et peut ralentir, voir même prévenir la progression de la maladie. Les objectifs de cette évaluation étaient de déterminer s'il y avait des changements dans la capacité aérobique (CA), la qualité de vie (QdV) et les niveaux d'activité physique (AP) après une intervention d'AP, et si ceux-ci étaient durables à long terme. Elle a également cherché à déterminer quels groupes de diagnostics en retiraient le plus grand bénéfice.
Méthodes : Une intervention d'AP de 6 semaines a été effectuée. Les patients ont subi des tests de dépistage de la CA (VO2 et marche de six minutes), de la QdV (questionnaire SF-36) et des taux d'AP (questionnaire R&G) au départ, immédiatement après l'intervention, puis six et douze mois après l'intervention.
Résultats : Actuellement, 383 patients sont inscrits et présentent des diagnostics répartis dans 6 catégories différentes (cancer, VIH/SIDA, troubles cardiométaboliques, respiratoires, neuromusculaires et troubles mentaux). Les personnes atteintes d'une maladie respiratoire ont commencé l'intervention avec la CA la plus faible, tandis que celles atteintes de troubles mentaux avaient la QdV de base la plus faible. Les taux d'AP au début de l'intervention étaient remarquablement bas (67 % d'inactivité) et ne différaient pas selon le groupe de diagnostic. Pour les 275 patients qui ont terminé l'intervention, un changement significatif ($p<0,05$) a été déterminé pour tous les résultats. Les personnes atteintes de troubles mentaux ont connu la plus forte augmentation de leur score de QdV et celles atteintes d'un cancer ont connu le changement le plus important dans les taux d'AP. Seulement 34 % des patients ont été classés comme inactifs immédiatement après l'intervention, ce qui a été maintenu 12 mois après l'intervention. L'augmentation initiale de la VO2 (+10%) n'était plus significative après 12 mois, mais un changement durable a été observé dans le test de marche de 6 minutes. La qualité de vie physique est restée élevée et s'explique en grande partie par les taux d'AP, tandis que la qualité de vie mentale est revenue au niveau de base.
Conclusion : Une intervention de 6 semaines peut induire des changements à long terme dans les taux d'AP et de la CA chez un large éventail de patients atteints de maladies chroniques. L'augmentation des niveaux d'AP à son tour peut entraîner une augmentation de la QdV physique.

Mots clés : activité physique ; maladie chronique ; qualité de vie ; capacité aérobique ; intervention d'exercice.

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List of Abbreviations

In Order of Appearance:

PA	....	Physical Activity
WHO	....	World Health Organization
UK	....	United Kingdom
QoL	....	Quality of Life
COPD	....	Chronic Obstructive Pulmonary Disorder
IPAQ	....	International Physical Activity
Questionnaire		
HIV	....	Human Immunodeficiency Virus
VO_2	....	Volume of Oxygen
RCT	....	Randomized Control Trial
CD4	....	Cluster of Differentiation 4
CIMS	....	Centre d'Investigation en Médicine du
Sport		
R&G	....	Ricci & Gagnon Questionnaire
IMAP	....	Integrative model of age-performance
BMI	....	Body Mass Index
ICD	....	International Classification of Disease
ATC	....	Anatomical Therapeutic Use
HS	....	High School
IQR	....	Interquartile Range
AIC	....	Akaike Information Criterion
ICC	....	Intra-class Coefficient
WHOQOL	....	World Health Organization Quality of Life
QALY	....	Quality adjusted life years

Figures, Tables, and Equations

1. Introduction

1.1 Physical Activity in the Population

Awareness of the decreasing levels of physical activity (PA) in the global population has existed for many years.[1] This is attributed to many lifestyle changes, such as transportation methods and increased urbanization.[2, 3] The rising number of people who work in desk jobs has also altered PA levels.[4, 5] In France specifically, the PA guidelines published by Public Health France (Santé Publique France) recommend that adults spend at least 30 minutes/day for 5 days/week completing moderate-to-vigorous activity, with strength training exercises at least 2 days/week, and stretching exercises 3 days/week.[6] Unfortunately, only 50.6% of French adults report being physically active during their leisure time and only 42.5% of adults currently attain levels of PA that allow for health benefits to occur.[7] This is lower than the global average 59.4%, based on data generated for 145 countries and 14 World Health Organization (WHO) subregions.[8] Raising this number is of great importance as the health benefits of PA are numerous. They include increased cardiorespiratory and muscular fitness, bone health, increased functional health, and improved cognitive ability.[9, 10]

Conversely, long periods with low PA (time spent sedentary) are linked to many health detriments, including all-cause mortality, development of chronic diseases, and an increased risk of falling.[9, 11] These detriments are present regardless of whether the subject also engages in periods of high PA.[12] Thus, it is important to not only increase PA levels but decrease bouts of sedentary time. Public Health France recommends that bouts of sitting and lying be broken up with walking to ensure that sedentary periods span no more than 2 hours at one time.[6] However, in spite of these guidelines, sedentary time is still on the rise, as screen time increases throughout all population groups, and occupational sedentary time continues to escalate.[5, 13-16] According to a study published in *The Lancet* by Lee et al., sedentary time can be attributed to 5.3 million deaths worldwide every year through both all-cause mortality and the chronic diseases that stem from low PA.[11] In France specifically, low PA was associated with 5.4% of coronary heart disease. It was attributed to 6.7% of type 2 diabetes and 9.6% of both breast and colorectal cancer.[11] Overall, lack of PA was linked to 8.7% of all-cause mortality. Thus, it is pertinent that people participate in PA as a prevention tool against the development of chronic diseases. But is this still the case after a chronic disease develops?

1.2 Activity Levels in People with Chronic Diseases

According to the WHO, chronic diseases contributed to approximately 46% of the global burden of disease in 2001.[17] A more recent paper, published in 2015, showed that chronic diseases have increased significantly, by 54.2%, between 1990 and 2013, with an age standardized increase of 1.4%.[18] Within France alone, there are roughly 10 million people currently living with a chronic disease, which equates to 15% of the population.[10] For a large part of the 20th century, bedrest, not PA, was prescribed for these people; in fact, PA was even seen as detrimental.[19] However, in the last 70 years a vast amount of evidence has been gathered that demonstrates the benefits of PA for people with chronic diseases. This began with a large epidemiological paper in 1953 published by Jeremiah Morris, who has since been labeled the father of PA epidemiology.[20] Unfortunately, the level of PA in this population remains low. A study conducted in Canada in 2009 showed that only 23% of elderly people with chronic diseases met the PA guidelines, significantly lower than the group with no chronic disease.[21] In a large UK study published in 2019, participants with a chronic disease over the age of 40 completed 51 minutes/week less moderate PA and 3 minutes/week less vigorous PA than their healthy peers.[22] The most drastic differences were seen in the group with mental health conditions where participants spent on average 2.5 hours/week less in moderate PA than their healthy peers, and in the cardiovascular group who spent the lowest amount of time on average in vigorous PA.[22] Thus, specific focus on this population is required, especially as the number of people with chronic diseases rises, with the WHO predicting that chronic diseases will be associated with 73% of all deaths and 60% of the global burden of disease by 2020.[17]

1.3 Effects of Physical Activity Interventions in People with Chronic Diseases

In attempts to increase the levels of PA in people with chronic diseases, many PA interventions have been performed, and systematic reviews compiled to determine a consensus in the overall findings.[23-27] These interventions have focused on a variety of chronic diseases and have ranged from a few weeks to several months. They have included a plethora of activities, along with mentoring opportunities, and they continue to be conducted due to the incontrovertible evidence that PA provide benefits to this population.[28] A large number of these interventions have been randomized control trials, but many have also been prospective cohort studies. The results of these interventions are affected by length, type of intervention, and by the chronic disease group that the intervention targets. Currently, there is some discrepancy, due to intervention differences, on whether PA level changes are sustained long-term, whether changes in quality of life (QoL) exist, and if the disease course is altered.

1.3.1 Long-term physical activity changes

Almost all studies evaluating long-term changes in PA agree that interventions evoke a short-term spike in PA levels but that reductions in adherence to PA occur post intervention.

However, there is disagreement surrounding whether patients return all the way to baseline levels or are able to maintain a lifestyle with slightly elevated PA levels. A study with chronic obstructive pulmonary disease (COPD) patients showed that after 12 months any changes observed in light physical activity immediately after the intervention, as measured by an accelerometer, were not sustained.[29] This is in contrast to breast cancer patients, who maintained higher levels of PA after an intervention, supported by both accelerometer and self-reported questionnaire. However, they were only assessed at one time point, 3 months post intervention.[30] Another study conducted on patients with cardiovascular disease had an intervention that included 120 minutes of walking/week and a sociocultural gathering once/month.[31] The intervention spanned the course of 9 months, but the authors found adherence to regular physical activity was still higher two years post intervention using the International Physical Activity Questionnaire (IPAQ) questionnaire.

1.3.2 Aerobic capacity

Many studies have shown improvements in aerobic capacity following PA interventions, although once again with mixed results on the lasting impacts.[28] In addition, one study found that these changes were only present immediately post-intervention for the group of diabetes patients who engaged in high-intensity activity, and not for those in the moderate-intensity group.[32] In a study by Coultas et al. on COPD, the findings demonstrated that patients in the intervention group maintained a 6 minute walking distance that was significantly higher than their initial level,[33] and in 2 other studies breast cancer survivors saw an increase in aerobic fitness that was still statistically significant 3 months post intervention.[30, 34] For patients with human immunodeficiency virus (HIV), similar changes were seen in aerobic capacity assessed with maximum rate of oxygen consumption (VO_2) post intervention, although no documentation was made about lasting impacts.[35] Only 2 of 5 studies reviewed in a meta-analysis on mental disorders and PA demonstrated an increased exercise capacity in this population.[36] These discrepancies are due to methodological differences, as well as sample size issues, and do not provide conclusive results.

1.3.3 Quality of life

The effects of a PA intervention on QoL are not conclusive. In a systematic review of patients with coronary heart disease, no difference was seen between controls and intervention participants.[37] Whereas, studies in breast cancer patients have shown improved QoL from supervised PA interventions.[30, 34, 38-40] Increases in PA were also associated with benefits in QoL in a study on patients with COPD and in pooled meta-analyses on patients with HIV and mental disorders.[35, 36, 41] The use of different measurement tools that evaluate different aspects of QoL makes comparisons between studies difficult.

1.3.4 Disease progression

Large benefits have been seen for cardiovascular patients after PA interventions. A systematic review and meta-analysis of 48 different cardio-metabolic studies showed a significant reduction in premature death upon increasing PA, along with a slowing of the progression of coronary artery disease and plaque reduction.[37] Another study saw a significant decrease in the number of adverse cardiovascular events in the intervention group compared to the control group.[31] For breast cancer patients, an increase in the chemotherapy completion rates was noted for participants of PA interventions compared to those with usual care.[42] However, in one study on diabetic patients, no change in insulin levels, fasting glucose, or fat mass occurred between the intervention and control group throughout the intervention.[43] In a recent HIV randomized control trial (RCT) that included 70 patients, significant improvements were seen after the intervention. The intervention group had an increased CD4 count while also improving their glucose levels, lean mass, and cholesterol levels.[44] The changes in disease progression have been strongly correlated with changes to PA levels, with a study in COPD patients demonstrating a parallel between the decline in PA levels and the worsening of lung function.[45] It is therefore vital that PA levels be sustained post-intervention to slow or potentially prevent disease progression.

1.4 Study Motivation

Currently, most primary studies have focused on only one specific chronic disease and have had a limited sample size. Systematic reviews have done well to synthesize the information, but meta-analyses are difficult to conduct due to different tests, different intervention protocols, different follow-up timelines, and different chronic diseases. The program conducted at Hôtel Dieu includes a wide variety of chronic diseases (heart disease, pulmonary disease, cancer, HIV/AIDS, etc.) allowing for comparison between disease groups. This will enable the researchers to determine if the current discrepancies within the literature stated above (whether PA level changes are sustained, whether changes in QoL exist, and if the disease course is altered), are due to differences in intervention design or due to difference between patients of different chronic diseases. The PA intervention also evaluates participants on a wide range of tests (aerobic tests, QoL measures, and self-reported PA level measures) which allows for a comprehensive understanding of the benefits of the intervention. The intervention itself is short and feasible, which if long-term lifestyle changes are sustained would indicate that 6-weeks is sufficient for an intervention.

1.5 Aims and Objectives

The two principle objectives of the evaluation where:

1. To determine if a PA intervention spanning 6-weeks instils long lasting PA behavioural changes in people with a chronic disease
2. To determine the short- and long-term effects of a 6-week PA intervention on the aerobic capacity, PA levels, and QoL of people with a chronic disease

The secondary objectives were:

1. To determine the differences and similarities in benefits from a PA intervention between the groups of chronic diseases and whether these groups act as effect modifiers in the link between the intervention and the outcomes.
2. To determine if the number of intervention sessions attended by participants played a role in the long-term success of the intervention
3. To determine if various medications, comorbidities, or additional risk factors act as confounding factors and affect the patient's outcome after the intervention.

2. Methods

2.1 Sample

Patients with a chronic disease who were undergoing a 6-week PA intervention at the Hôtel Dieu hospital were included in this evaluation. In order to be eligible to participate in the intervention, patients needed to be referred by their treating specialist, have a chronic disease listed on the "affections de longue durée 30", and be declared by a physician at the sports medicine clinic within Hôtel Dieu to be in poor physical condition. The intervention commenced January 2017 and is still ongoing. Patients who had entered the intervention before 1 April 2019 were used for analysis.

2.2 The Intervention

The intervention took place at the Centre de Réhabilitation par le Sport – Centre d'Investigation en Médicine du Sport (CIMS) at the Hôtel Dieu Hospital in Paris, France. It spanned 6-weeks. Each week participants attended 3 sessions/week lasting 1.5 hours each where they participated in a 15-minute warm-up, a 45-minute strength building activity, and a 30-minute cardiovascular activity. Having both aerobic and resistance training components in the intervention has previously been shown to be of high importance as changes in aerobic capacity and changes in strength affect different long-term outcomes on health.[46] Six of the sessions also included a 30-minute classroom component where participants were educated on various topics including healthy eating, heart rate, and long-term behaviour change. These sessions were led and monitored by a trained "Enseignant en Activité Physique Adaptée" (Teacher of Adapted Physical Activity). A doctor was available in case of any adverse event.

2.3 Outcome Measures

Tests were completed on all participants at four time points (1) pre-intervention, (2) post-intervention, (3) 6-months post-intervention and (4) 12-months post-intervention in order to assess both the short and long-term benefits of the intervention. Tests were divided into 5 categories that are displayed in Table 1.

Table 1. Tests Performed at Each Hospital Visit

Test	Description
Medical Tests	
Sports Medicine Consult	To ensure patient safety during the intervention
Specialist Consult	To monitor disease progression or reversion during the intervention
Anthropometric Tests	
Height and Weight	Measured in centimeters and kilograms
Muscle and Fat Mass	A scan performed to determine body composition
Bone Density	A scan performed to determine body composition
Waist/Hip Circumference	Measured in centimeters around the waist and hips
Aerobic Assessment	
VO2 Max Test	Max effort test completed on an ergo cycle
6 Minute Walk Test	Distance covered in 6 minutes of walking
Quality of Life Assessment	
SF-36	Quality of Life Questionnaire (Mental and Physical)
Activity Level Assessment	
Ricci & Gagnon	Questionnaire evaluating PA Score in Daily Life

Medical tests were conducted to monitor disease progression and ensure patient safety throughout the intervention. Anthropometric tests were completed as part of standard patient care and were used as potential explanatory variables in the analysis.

Three outcomes were of interest in this evaluation: 1) Aerobic Capacity, 2) QoL, and 3) PA Levels. These were assessed through 5 outcome measures. Aerobic capacity was assessed using both a VO_2 max test and 6-minute walk test. These two tests were highly correlated (68%) but were kept separate in analysis as different variables were explanatory and differing amounts of variation were present between the two variables.

The SF-36 Questionnaire was used to assess QoL throughout the intervention.[47] This questionnaire has previously been validated.[48] Two scores are generated from this test: a physical QoL score and a mental QoL score. These assess two substantially different components of QoL and were not merged to create a global QoL score as the balance between the components and their contributions to overall QoL are unknown.[49] The creators of the questionnaire also advise against the use of one global score.[50] Many previous studies have used this questionnaire allowing for comparison to the general population and other chronic disease groups.[51, 52]

Lastly, to assess the PA levels of participants outside of the intervention the Ricci & Gagnon Questionnaire (R&G) was administered.[53] The R&G returns a score between 0-40, with 40 representing the highest activity levels, and 0 representing the lowest sedentary activity levels. Persons with scores < 18 are considered to be inactive, while persons with scores between 18 and 35 are classified as active, and those with scores >35 are considered very active.[53] This questionnaire has not been validated, but a study that utilized both the R&G and the validated International Physical Activity Questionnaire saw those deemed inactive by the R&G had a significantly lower amount of vigorous activity than those who were classified as active by the R&G.[54] Several studies evaluating chronic disease patients have also used the R&G questionnaire. This includes a study on cancer patients following an exercise program and another study on a general group of chronically ill patients post hospital rehabilitation.[55, 56]

2.4 Potential Confounders, Effect Modifiers, and Mediators

Many parameters have previously been associated with aerobic capacity, QoL, and PA levels. These include, but are not limited to patient diagnosis, medications, age, sex, BMI, comorbidity scores, level of studies, baseline activity levels, tobacco consumption, and alcohol consumption.

2.4.1 Age

The age-aerobic capacity relationship has been well-researched. Aerobic capacity initially increases with age and then begins to decrease. Age was transformed using the integrative model of age-performance (IMAP) where α represents a performance increase at the level of cellular division and β represents the age-related decline of cell functionality in relation to time (t).[57]

Equation 1: Integrative model of age-performance (IMAP)

$$P(t) = \beta_0 N_\infty * e^{-\frac{\alpha_0}{\alpha_r} e^{-\alpha_r t}} * (1 - e^{\beta_r (t - t_d)})$$

As age-related increase was not applicable to this population due to a mean age of 59 years, the α-terms were not used to transform age. The transformed variable was an appropriate fit between age and aerobic capacity (VO_2 and six-minute walk test) in our sample as demonstrated in Figure 1. This transformed variable was therefore used in the aerobic capacity models.

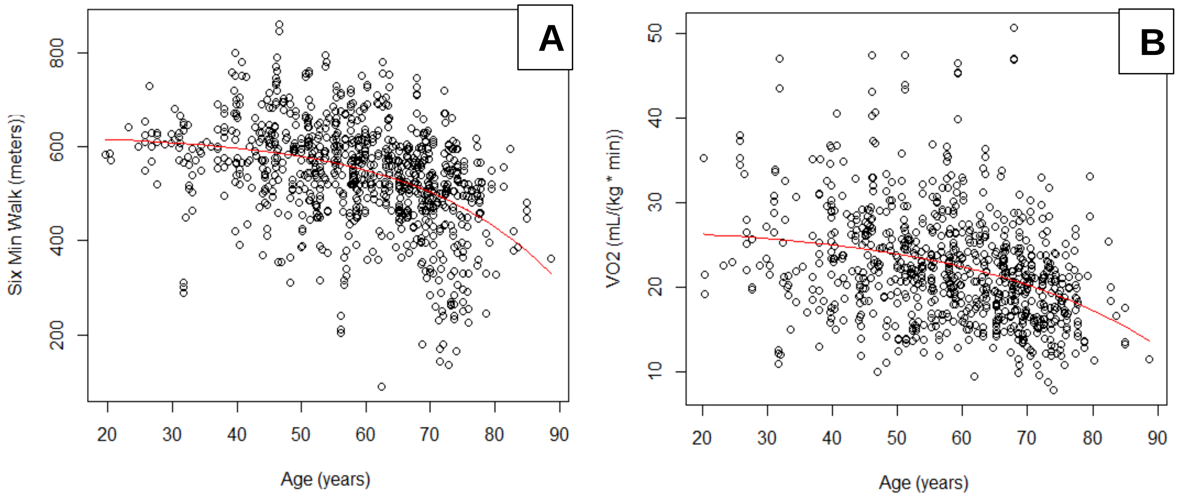


Figure 1. A. The relationship between age and the six-minute walk test using a modified integrative model of age-performance (IMAP) equation, displayed in Equation 1. B. The relationship between age and the VO_2 test using a modified IMAP equation, displayed in Equation 1.

The relationship between age and QoL has also been extensively researched. QoL is negatively affected by many things including: difficulty with everyday activities, limitations in mobility, long standing illness, and relatively poor financial situations, all of which have the potential to be mediated and moderated by age and differing chronic diseases.[58] Age-related activity declines have also been observed for moderate-intensity activity, but not for other intensity levels.[59] This decline was shown to be related to sex in a linear fashion. A non-transformed age variable was included in the models for SF-36 mental, SF-36 physical, and R&G.

2.4.2 Sex

Sex is strongly correlated to both aerobic and strength performance with men having statistically higher performance levels than women.[59] Men also tend to be more active than women.[60] Sex-related differences also exist in QoL related measures. One study showed that high QoL was associated with high SES, whereas this was not the case for women.[61] Another study, focused on those with heart failure, showed that women had a worse QoL when compared to men for physical function but found no difference in emotional distress.[62] It will therefore be evaluated as a confounder for all 5 outcome models, and as a potential effect modifier for the 2 QoL outcomes.

2.4.3 BMI

Body Mass Index (BMI) is also significantly related to aerobic capacity and could confound the effects of the intervention.[63] BMI affects physical aspects of QoL more than the mental aspects but is significantly associated with both.[64] Those with higher BMIs are also less likely to have high levels of PA. As such, it was taken into account as a potential confounder in all 5 outcome models.

2.4.4 Diagnosis

Diagnoses were collected from patient charts. Diagnosis codes are recorded by physicians using the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD) developed by the WHO.[65] All the codes for each patient were used for the generation of chronic disease groups. Six major groups of patients are seen by CIMS: 1) patients with cardio-metabolic diseases, 2) patients with cancer, 3) patients with HIV, 4) patients with respiratory diseases and sleep apnea 5) patients with mental disorders, and 6) patients with rheumatology and neuromuscular issues. A full list of classifications is shown in Figure 2. For some analyses, mental disorders were split into depression and other mental disorders due to varying modifying effects. Sleep apnea was also separated from other respiratory diseases in certain instances where the two diagnosis groups incurred significantly differing results.

These disease categories are not mutually exclusive, and participants could be included in more than one category. In order to factor the lack of mutual exclusivity into the analysis, a comorbidity score was generated. The ICD-10 codes were input into the R package "comorbidity" to generate a comorbidity score for each patient.[66] Two scores are commonly used to control for severity of illness: the Elixhauser score and the Charleson score.[67] The Elixhauser scoring system was used in this study because previous literature has shown it to be better at predicting mortality and health service use than the Charleson index in varying chronic disease populations.[68-70] It also allowed for a greater number of classifications to be included with 31 categories compared to the Charleson index that only has 17 groups.[67] Weighted scores were used to distinguish the severity of different diseases. These are constructed from work done by Moore et al. and Van Walraver et al. who assigned a score to each category based on mortality and hospital readmission risk.[71, 72]

Differing diagnosis groups were predicted to modify the results of the intervention due to differences in pathology, onset, and treatment.

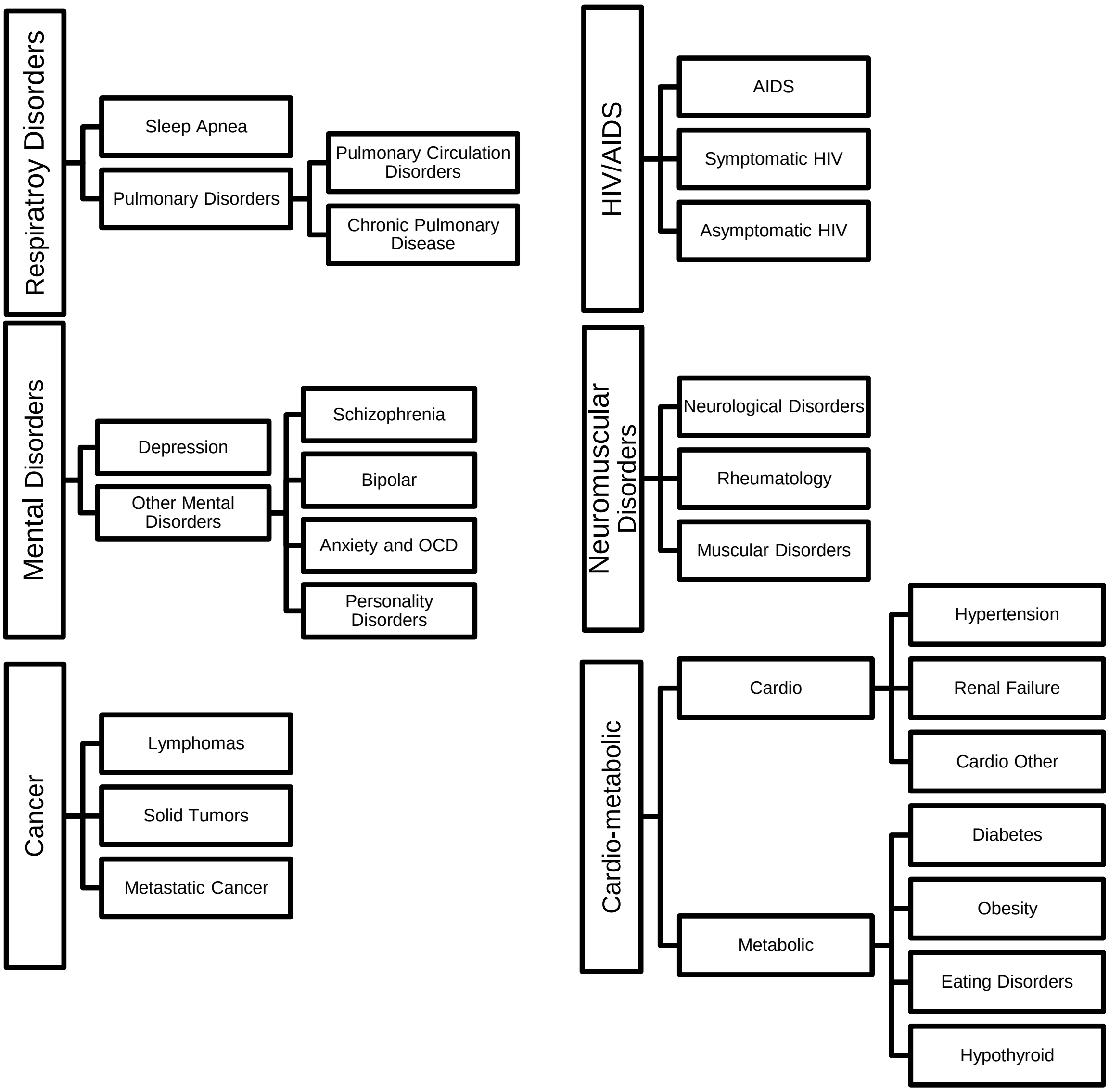


Figure 2. Diagnosis groups based on ICD-10 codes recorded in patient charts.

2.4.5 Medications

Medications were retrieved from patient clinic notes. The total medications for each patient was summed. Medications were also grouped according to the WHO classification system that uses the anatomical therapeutic chemical (ATC),[73] and the total number of medication types for each patient was tallied. Polypharmacy is a term used to describe the prescription of multiple medications. There is no definitive threshold for defining polypharmacy with papers using varying cutoffs, however a systematic review published in 2017 identified the most common definition to be 5+ medications.[74] Polypharmacy has previously been shown to be strongly related to QoL, with higher total medications associated with lower QoL.[75] Medication types have the ability to affect aerobic capacity. Inhalers tend to improve capacity in patients with COPD, whilst non-steroidal anti-inflammatory drugs can lead to increased breathlessness through fluid retention.[76] Various medication side effects could also cause changes in PA levels through nausea, drowsiness, or electrolyte derangement.[76]

2.4.6 Tobacco and Alcohol Consumption

Tobacco is quantified for each patient using the equation "packets/day * years". The clinic notes specify whether tobacco is currently used, previously used, or never used. Alcohol consumption is recorded in clinic notes if patients indicate consumption of more than 2 drinks per day. Both tobacco usage and alcohol consumption have been linked to lower aerobic performance and lower PA levels.[77, 78] The QoL of chronic disease patients is also affected by smoking and alcohol consumption.[79-82]

2.4.7 Other potential confounders

The level of education was retrieved for all patients and grouped into 3 categories 1) less than a high school diploma, 2) high school diploma, and 3) tertiary studies. Secondary and tertiary education have previously been associated with a higher QoL and were therefore included in the two-by-two analysis for the two SF-36 outcomes.[83] There was no evidence that education affects aerobic capacity but it potentially affects PA levels through knowledge of health benefits and PA guidelines.[84] If education level was strongly associated with socioeconomic status, PA levels might also be affected through neighbourhood safety and free-time.[84]

The number of sessions attended within the intervention was also examined for potential effects on the outcome variables. Researchers were interested in determining if a relationship existed between the number of attended sessions and the outcome variables, or if a threshold number of sessions exists that explains changes in the outcome variables.

2.5 Ethical Approval

Formal ethics approval for this study was not required from the University of Sheffield Ethics Committee as the study utilized secondary data. A declaration form has been completed and supporting documents have been obtained (Appendix 1). Only hospital patients that consented to the use of their data for research purposes where included in the analysis and all data was anonymized. Authorization for IRMES to use the data was provided by Assistance Publique - Hôpitaux de Paris.

2.6 Statistical Analysis

Statistical analysis was carried out using R software (Version 3.5.2).[85] Statistical significance was set at $p<0.05$.

2.6.1 Imputation

For variables with missing data, where the missing values were deemed to be missing at random, imputation was conducted to replace the missing data with substituted values. This included the following variables: VO_2 test, six-minute walk test, SF-36 questionnaire, R&G questionnaire, BMI, and tobacco consumption. For all these variables, the amount of missing data was below 25%, which is recommended to ensure the variance structure.[86] Imputation was completed using the 'mice' package in R.[87] A predictor matrix was created based on significantly correlated variables. The imputation was run 5 times and imputations were pooled for all regression analyses. Multiple imputation was done instead of using a single imputation as this allows for a better estimate of the uncertainty and variance associated with imputing the data.[88] Plots and tests from the R package "mitools" were conducted to ensure the multiple imputation was successful and did not bias the results.[89]

2.6.2 Descriptive Statistics and Baseline Analysis

Descriptive statistics were completed using frequency tables and median (IQR) calculations. Generalized linear models were made for the 5 aforementioned outcome variables (VO_2, six-minute walk, SF-36 physical, SF-36 mental, and R&G). To determine which variables to include in the regression Pearson or spearman correlations were conducted for continuous variables and Students' T-tests or Wilcoxon-Rank tests were conducted for instances where the explanatory variable was binary. All tests with p-values under 0.2 were included in the starting generalized linear model. A backward stepwise approach was used, to achieve the model with the lowest AIC number and thus, best fit. Effect modification was tested through interaction terms within the model. The assumptions of each model were tested with the tests used outlined in Appendix 2.

For VO_2, 3 outliers were present in the data. These outliers had significantly higher VO_2 values compared to the mean, with scores that would not be classified as having a poor aerobic condition.[90] They were included in the study because of low PA scores in their daily lives. When these 3 outliers were removed from the regression, the assumptions of the regression were met, however the coefficients of the regression did not change greatly. The model statement of the initial regression, with all variables that had $p< 0.2$, for VO_2 was as shown in Equation 2. Inclusion of all variables with $p<0.2$ in the initial model was to ensure that no interactions between explanatory variables were missed.

Equation 2. Initial Baseline Regression Equation including all variables with p <0.2

$$VO_2 = \alpha_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_5 x_5 + \beta_6 x_6 + \beta_7 x_7 + \beta_8 x_8 + \beta_9 x_9 + \beta_{10} x_{10} + \beta_{11} x_{11} + \beta_{12} x_{12} + \beta_{13} x_{13} + \beta_{14} x_{14} + \beta_{15} x_{15}$$

$\alpha_0 = intercept$

$x_1 = sex\ (binary{:}\ reference\ is\ female)$

$x_2 = age\ (continuous)$

$x_3 = BMI\ (continuous)$

$x_4 = number\ of\ medications\ (continuous)$

$x_5 = weighted\ comorbidity\ score\ (continuous)$

$x_6 = current\ level\ of\ physical\ activity\ as\ assessed\ by\ R\&G\ questionnaire\ (continuous)$

$x_7 = tobacco\ consumption\ (continuous)$

$x_8 = cancer\ (binary{:}\ reference\ is\ no\ cancer\ diagnosis)$

$x_9 = cardiometabolic\ (binary{:}\ reference\ is\ no\ cardiometabolic\ diagnosis)$

$x_{10} = respiratory\ (binary{:}\ reference\ is\ no\ respiratory\ diagnosis)$

$x_{11} = sleep\ apnea\ (binary{:}\ reference\ is\ no\ sleep\ apnea\ diagnosis)$

$x_{12} = HIV\ (binary{:}\ reference\ is\ no\ HIV\ diagnosis)$

$x_{13} = mental\ disorder\ except\ depression\ (binary{:}\ reference\ is\ no\ mental\ disorder\ diagnosis)$

$x_{14} = depression\ (binary{:}\ reference\ is\ no\ depression\ diagnosis)$

$x_{15} = neuromuscular\ (binary{:}\ reference\ is\ no\ neuromuscular\ diagnosis)$

For the six-minute walk test, outliers were also present. One patient walked significantly more than the rest and one walked significantly less. The patient who walked significantly less was shown to have only completed 2 of the 6 minutes of walking due to low O_2 saturation and was removed from the analysis. The patient who walked significantly more was included in the intervention due to low PA level scores. When removed, it had little influence on the coefficients of the regression but allowed the assumptions of the regression to be met. The six-minute walk test was strongly negatively skewed. To compensate for this a squared transformation was performed on the outcome variable.

For the QoL data obtained from the SF-36, a squared transformation was conducted for the mental score to correct for a negative skew, whilst the physical score required no corrections for all the regression assumptions to be met. The R&G score was positively skewed and corrected through a log transformation to achieve normality.

T-tests and chi-squared tests were also conducted between patients who were lost to follow up and patients who remained in the study to assess for a difference between groups that could lead to bias in the outcomes.

2.6.3 Pre/Post Intervention Analysis

A subset of participants was created to remove those who were still in the process of completing the intervention and had not yet completed the post-intervention tests. Paired t-tests were conducted for all outcome variables to establish whether a significant difference existed between pre-intervention and post-intervention. A significant difference was observed for all 5 outcome variables. A generalized linear regression was performed with absolute change as the outcome variable (outcome at time point 2 – outcome at time point 1) to determine if any diagnosis group experienced a significantly different change and what variables explained a significantly smaller or larger mean change.

Variables were once again added to the regression based on 2x2 significance. For all continuous variables, centering was conducted so that the intercept reflected the mean change when all binary variables were 0, and all significant explanatory variables represented deviations from the mean. A backwards stepwise regression was once again conducted to determine the best model. All model statements included similar explanatory variables and an example model statement for physical activity levels assessed by the Ricci & Gagnon question is included in Appendix 3.

Tests of the regression assumptions were conducted. For change in VO_2 all the assumptions were met. The six-minute walk test did not meet the assumptions due to a large number of outliers in the data. Outliers present here, but not in the VO_2 are most likely due to acute musculoskeletal pains that exist at one of the two appointments and therefore do not represent a true test. These pains are not present on the bicycle ergometer and thus, abnormally large changes between the two visits do not exist for VO_2.

The SF-36 physical component met all the assumptions. The mental component had a slightly negative skew but graphically appeared to meet all assumption requirements. The R&G score had a negative kurtosis value, but this can be attributed to the scoring system, and graphically it still met all the assumptions of the generalized linear regression.

2.6.4 Longitudinal Analysis

For the subset of participants who had completed the 12-month post-intervention visit, a mixed effects model was used to allow for the unknown correlation between the outcomes within each patient which violates the independent errors assumption of a normal model. This model allows for time varying information and for outcome variables to be assessed over the 4 visits to determine if patients return to baseline levels after the intervention or maintain at an elevated level. The model statement for the six-minute walk test is included below as an example (Equation 3).

Equation 3. Mixed Effects Model for Six Minute Walk including all variables with p <0.2

$$six\,min\,walk = (\alpha_0|factor) + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_5 x_5 + \beta_6 x_6 + \beta_7 x_7 + \beta_8 x_8 + \beta_9 x_9 + \beta_{10} x_{10} + \beta_{11} x_{11} + \beta_{12} x_{12} + \beta_{13} x_{13} + \beta_{14} x_{14} + \beta_{15} x_{15} + \epsilon_i$$

$\alpha_0|factor = intercept - random\ intercept\ given\ for\ each\ study\ participant$

$x_1 = sex\ (binary: reference\ is\ female)$

$x_2 = age\ (continuous)$

$x_3 = BMI\ (continuous)$

$x_4 = number\ of\ medications\ (continuous)$

$x_5 = weighted\ comorbidity\ score\ (continuous)$

$x_6 = current\ level\ of\ physical\ activity\ as\ assessed\ by\ R\&G\ questionnaire\ (continuous)$

$x_7 = cancer\ (binary: reference\ is\ no\ cancer\ diagnosis)$

$x_8 = cardiometabolic\ (binary: reference\ is\ no\ cardiometabolic\ diagnosis)$

$x_9 = respiratory\ (binary: reference\ is\ no\ respiratory\ diagnosis)$

$x_{10} = sleep\ apnea\ (binary: reference\ is\ no\ sleep\ apnea\ diagnosis)$

$x_{11} = HIV\ (binary: reference\ is\ no\ HIV\ diagnosis)$

$x_{12} = mental\ disorder\ except\ depression\ (binary: reference\ is\ no\ mental\ disorder\ diagnosis)$

$x_{13} = depression\ (binary: reference\ is\ no\ depression\ diagnosis)$

$x_{14} = neuromuscular\ (binary: reference\ is\ no\ rheumatological/neuromuscular\ diagnosis)$

$x_{15} = visit\ number\ (categorical: reference\ is\ baseline\ visit)$

$\epsilon_i = error\ term$

The assumptions of the mixed model were confirmed through a histogram of the residuals to determine normality, a plot of the residuals against the fitted values to establish that the errors of constant variance, and plots of the explanatory variables against the residuals to determine a linear response. To determine if the errors were independent of each other a scale-location plot was made. The graphs for all the linear mixed models appeared to meet assumptions.

3. Results

3.1 The Population

Between 1 January 2017 and 31 March 2019, 383 people with chronic diseases entered the intervention program at the Hôtel Dieu Hospital (Figure 5).

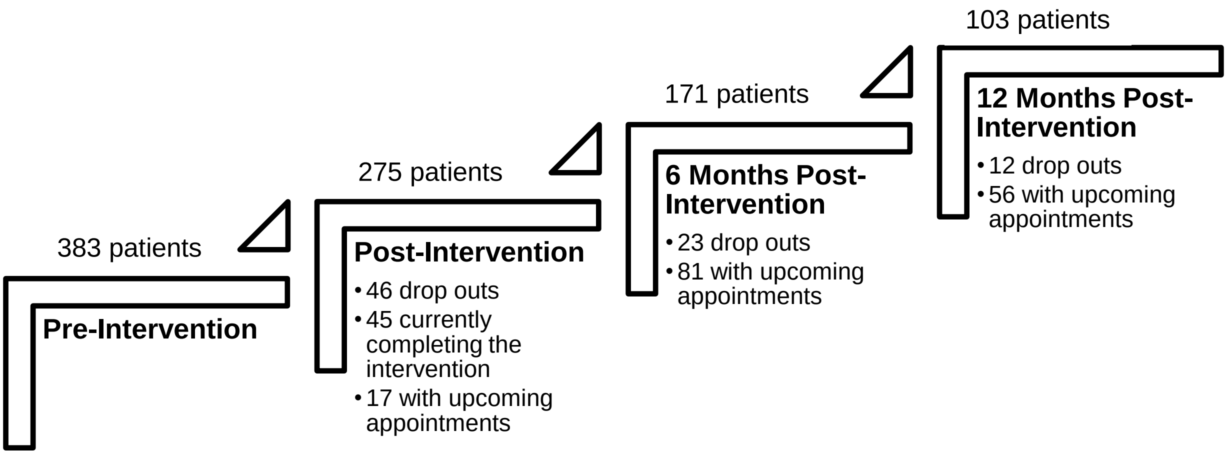


Figure 3. Number of patients currently enrolled in the intervention at Hôtel Dieu.

These patients were highly heterogeneous, ranging greatly in age, BMI, and comorbidities. Their baseline characteristics by diagnosis grouping are displayed in Table 2. Those with mental disorders and HIV were significantly younger than those without a mental disorder or HIV, whilst those with cancer, respiratory diseases and cardio-metabolic diseases were significantly older than those without ($p < 0.01$). Those with cardio-metabolic diseases had a significantly higher BMI, whilst those with cancer and respiratory disease had significantly lower BMIs ($p < 0.01$). Those with cancer and respiratory diseases had higher weighted comorbidity scores, whilst those with cardio-metabolic diseases, mental disorders, and HIV had a statistically lower score ($p<0.01$). Cardio-metabolic patients took a significantly higher amount of medications and those with cancer took a significantly lower amount of medication ($p< 0.01$).

3.2 Loss to follow up

Of the 383 people who began the intervention, 81 (21%) were lost to follow up throughout the duration of the year. The 3 main reasons listed for these dropouts include medical reasons, lack of commitment to the intervention, and social reasons. As this intervention was not conducted as a study but rather as part of patients' standard of care treatment, prescribed by their treating physicians, a retention rate of 79% was deemed to be highly effective at participant retention. Longitudinal studies with detailed consent procedures and patient awareness often report attrition rates between 30% – 70%, and anything less than 20% is considered to be a high retention rate.[91, 92]

Those who were lost to follow up were compared to those who remained for outcome and explanatory variables. There was no statistically significant difference in baseline VO2, six-minute walk, R&G score, age, BMI, sex, or diagnosis. A slight difference existed within the SF-36 questionnaire, with drop-outs having lower scores than those who remained in the intervention.

3.3 Multiple Imputations

The success of the multiple imputations was assessed both graphically and statistically. Density plots (Figure 4), strip plots, and correlation plots were all visually acceptable. Kruskal-Wallis tests conducted to compare the distribution of each imputation set and the original data all returned non-significant values demonstrating no difference in the distributions. All values of the Gelman-Rubin convergence statistic ($\hat{R}$) were below 1.1 indicating convergence of the imputations, which occurs at $\hat{R}$ = 1.[93]

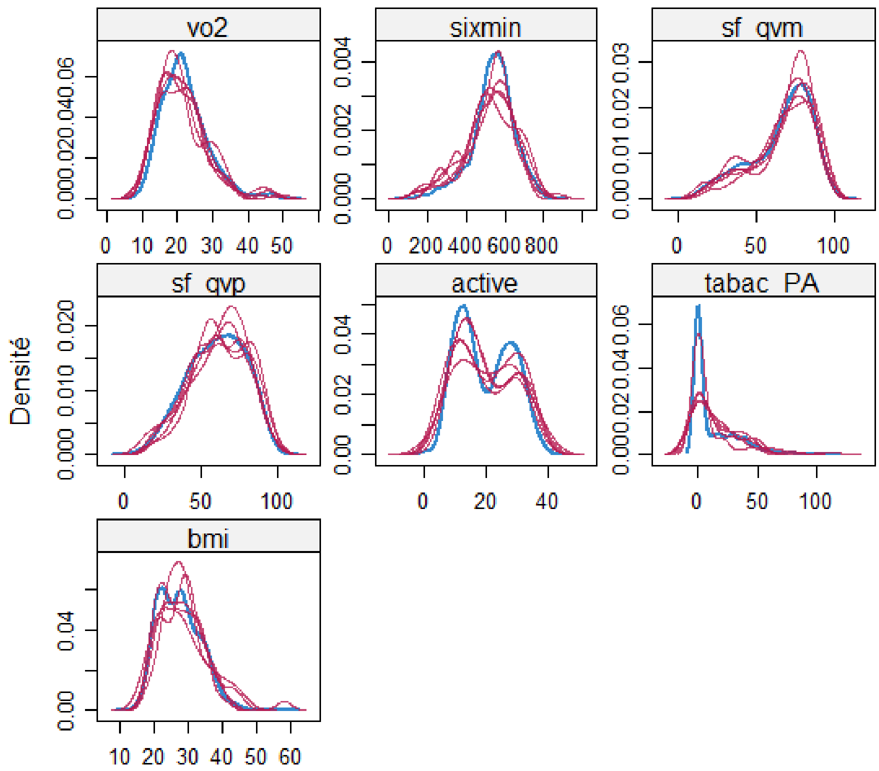


Figure 4. Density plots for all imputed variables.

The non-imputed density is shown in blue and the 5 imputed densities are displayed in red. All the density plots follow similar patterns demonstrating that the multiple imputations were completed successfully.

Table 2. Baseline Descriptive Statistics by Diagnosis

	All	Cancer	HIV/AIDS	Resp Disease	Cardio-metabolic	Mental Disorders	Neuromuscular
Number of Patients	383	135	53	80	203	48	39
Age [a]	59.2 (47.9-69.1)	63.1 (52.2-70.4) *	50.4 (44.0-58.7) *	68.4 (54.5-73.2) *	61.9 (50.8-70.4) *	49.2 (38.0-61.3) *	61.0 (51.2-71.8)
BMI [a]	26.8 (22.6-31.8)	23.5 (20.9-27.2) *	27.9 (23.7-32.2)	25.3 (20.9-29.6) *	29.5 (25.9-34.9) *	28.0 (22.5-31.9)	26.9 (22.5-31.5)
Male/Female [b]	42.8/57.2	46.7/53.3	47.2/52.8	40.0/60.0	45.0/55.0	22.9/77.1 *	30.8/69.2
Level of Studies [b c] (<HS/HS/>HS)	9.6/15.9/74.5	5.8/11.7/82.5 *	20.0/20.0/60.0 *	6.9/11.9/81.4	14.6/18.1/67.3 *	2.6/18.4/79.0	3.2/9.7/87.1
Types of Medications [a d]	2.0 (1.0 – 4.0)	2 (1 – 3.5)	2.0 (1.0 – 4.0)	3.0 (2.0 – 4.0) *	3.0 (2.0 – 5.0) *	3.0 (2.0 – 4.0) *	2.0 (1.0 – 3.5)
Total Medications [a]	4.0 (2.0 – 6.0)	3 (1 – 5) *	4.0 (3.0 – 7.0)	5.0 (3.0 – 8.0) *	5.0 (3.0 – 8.0) *	5.0 (3.0 – 6.5)	4.0 (2.0 – 6.0)
Comorbidity Score [a e]	13.0 (10.0 – 18.0)	18.0 (17.0 – 18.0) *	11.0 (10.0 – 11.0) *	14.0 (13.0 – 14.0) *	10.0 (7.0 – 16.0) *	6.0 (5.0 – 11.5) *	12.0 (11.0 – 16.0)

a – Median (IQR)
b – Frequency (%)
c – <HS = less than a high school diploma; HS = high school diploma; > HS = tertiary education
d – Medications classified using the anatomical therapeutic chemical (ATC) classification system from the WHO[73]
e – Using the Elixhauser scoring system and ICD-10 codes [65, 67, 71, 72]
* – Those with the diagnosis are significantly different to those not in the diagnosis group ($p < 0.05$)

3.4 Initial Outcome Values

Baseline aerobic capacity was low in this population. The median (IQR) VO_2 was 20.5mL/min/kg (16.8 mL/min/kg – 23.8 mL/min/kg), which is classified as ‘very poor’ or ‘poor’ according to VO_2 normative data.[90] The median (IQR) of the six-minute walk was also low, 530m (461m – 595m), again below norms. Similar explanatory variables were present in both aerobic tests. Men, younger patients, and patients with lower BMI all had higher aerobic capacities. Those who took fewer medications and had higher PA levels also had higher aerobic capacities. For just the VO_2 test, tobacco consumption was significantly related to a lower aerobic capacity. Those with respiratory disease had a lower aerobic capacity than those without a respiratory condition, and those with mental illness had a higher capacity compared to those with other chronic conditions as shown in Table 3.

Table 3. Generalized Linear Regression for Baseline Aerobic Capacity (VO_2 and Six-Minute Walk) with Significant Explanatory Variables.

	VO_2 [a]		Six-Minute Walk [b]	
	β	p-value	β	p-value
Intercept	14.43	$p < 0.001$	170.24	$p < 0.001$
Sex (ref: female)	4.11	$p < 0.001$	40.33	$p < 0.001$
Age (transformed) [c]	0.58	$p < 0.001$	0.78	$p < 0.001$
BMI	- 0.30	$p < 0.001$	- 2.94	$p < 0.001$
Total Medication Number	- 0.35	$p < 0.001$	- 8.88	$p < 0.05$
Baseline Activity Level [d]	0.17	$p < 0.001$	2.69	$p < 0.001$
Tobacco (Packets/Day * Years)	-0.04	$p < 0.01$		
Respiratory Disease (ref: none)	- 3.22	$p < 0.001$	- 70.74	$p < 0.001$
Mental Disorder excluding Depression (ref: none)	2.02	$p < 0.05$		
Depression (ref: none)			39.76	$p < 0.05$
Adjusted R^2	0.46	$p < 0.001$	0.42	$p < 0.001$

Models of aerobic capacity assessed by VO_2 and six minute walk test; The independent variables explained 46% of the variance in VO_2 and 42% of the variance in the six-minute walk test

[a] VO_2 measured in mL/min/kg

[b] Six-minute walk test measured in meters. All β coefficients have been de-transformed from their squared form to allow for ease in interpretation

[c] Age transformed using IMAP

[d] Assessed through R&G Questionnaire.

Patients had a higher mental QoL score than physical QoL score at baseline, with a median (IQR) of 67/100 (45/100 – 78/100) for the mental score and of 55/100 (43/100 – 70/100) for the physical score. The SF-36 showed different predictors for mental and physical QoL (Table 4). Sex and baseline PA levels were significantly associated with both QoL scores and those with sleep apnea had a lower QoL overall than other diagnosis groups. Patients with a respiratory disease had lower physical QoL, whilst those with mental disorders and depression had a significantly lower mental QoL. Only 15% of the variance for baseline QoL was explained with these parameters.

Table 4. Generalized Linear Regression for Baseline Quality of Life (Mental and Physical) with Significant Explanatory Variables.

	Mental QoL [a]		Physical QoL	
	β	p-value	β	p-value
Intercept	47.06	$p < 0.001$	52.16	$p < 0.001$
Sex (ref: female)	28.66	$p < 0.01$	9.65	$p < 0.001$
Age (years)	3.89	$p = 0.105$		
Baseline Activity Level [b]	7.67	$p < 0.001$	0.32	$p < 0.05$
Total Medication Number			- 0.94	$p < 0.01$
Sleep Apnea (ref: none)	-40.69	$p < 0.05$	- 14.96	$p < 0.01$
Respiratory Disease (ref: none)			- 6.71	$p < 0.01$
Mental Disorders excluding Depression (ref: none)	- 33.90	$p < 0.05$		
Depression (ref: none)	- 31.42	$p < 0.05$		
Adjusted R^2	0.15	$p < 0.001$	0.15	$p < 0.001$

Models of QoL assessed by the SF-36; the independent variables explained 15% of the variance in both mental and physical QoL
[a] All β coefficients have been de-transformed from their squared form to allow for ease in interpretation
[b] Assessed through R&G Questionnaire.

At baseline, the PA levels in this group were dismal, with 67.9% being classified as inactive by the R&G questionnaire. Age, sex, BMI, and diagnosis were all not significantly related to the level of PA, with only the number of medications having statistical significance. Only 3% of the variance in PA levels was explained by the number of medications.

3.5 Intervention Effects

Large changes in aerobic capacity were seen post-intervention for the 275 patients who had finished the intervention and had completed their second set of testing. The paired t-test for VO_2 showed a mean absolute change of 1.8 mL/min/kg ($p < 0.001$) between the two visits. Of the initial 131 people who had a VO_2 classified as ‘very poor’, 30 improved their VO_2 rating to a higher category. An absolute change of 31.8m was also present for the six-minute walk ($p < 0.001$). Those with lower aerobic scores before the intervention had larger absolute changes in VO_2 (Table 5). Age and the total number of medications were also significantly related, with a non-significant trend between those with cardio-metabolic disease having a lower VO_2 change than those without the disease.

Table 5. Generalized Linear Regression for Absolute VO_2 Change with Significant Explanatory Variables.

	β	p-value
DV: Pre/Post VO_2 Change		
Intercept	1.79	$p < 0.001$
Sex (ref: female)	1.00	$p = 0.07$
Mean Centred Age (transformed) [a]	0.26	$p < 0.05$
Mean Centred Total Medication Number	- 0.14	$p < 0.05$
Mean Centred Baseline VO_2	- 0.14	$p < 0.01$
Cardio-metabolic Disease (ref: none)	- 0.93	$p = 0.08$
Adjusted R^2	0.08	$p < 0.001$

Explanatory variables that are associated with an absolute change in VO_2 after the intervention
[a] Age was transformed using the IMAP equation.

Positive changes in QoL were also seen after the intervention, with a mean change of 8.3 points in the physical component of the SF-36 and a mean change of 7.9 points in the mental component of the SF-36. A larger amount of variance was explained with the independent variables in the SF-36 mental component (34%) compared to the physical component where only 20% of the variance for the absolute change was explained (Table 7). Once again, those with lower baseline scores had a significantly larger change than those with scores above the mean. Those with depression and other mental illnesses had a significantly higher increase in their mental QoL scores compared to other groups, accounted for in the regression through low baseline scores. There was a 5.5-point change in PA levels (on a 40-point scale) after the intervention, decreasing the number of inactive patients from 67.9% to 34.2% (Figure 5). This change in PA levels was highly significant and was significantly related to the number of intervention sessions attended by the patient ($p< 0.01$) and to their baseline PA level ($p < 0.001$). Patients with a diagnosis of cancer had a larger self-reported change in PA levels than the rest of the diagnosis groups ($p <0.05$). These three explanatory variables explained 34% of the variance in the absolute change of PA levels.

Table 6. Generalized Linear Regression for Absolute QoL Changes with Significant Explanatory Variables.

	SF-36 Mental		SF-36 Physical	
	β	p-value	β	p-value
Intercept	7.19	$p < 0.001$	8.86	$p < 0.001$
Sex (ref: female)	3.94	$p < 0.05$		
Mean Centred BMI	0.33	$p = 0.05$		
Mean Centred Total Medication Number	- 0.80	$p < 0.05$	- 0.81	$p < 0.05$
Mean Centred Post-Intervention Activity Score[a]	0.27	$p < 0.05$	0.25	$p < 0.05$
Mean Centred Baseline SF-36 Score	- 0.48	$p < 0.001$	- 0.36	$p < 0.001$
Depression (ref: none)	6.23	$p = 0.15$		
Adjusted R^2	0.34	$p < 0.001$	0.20	$p < 0.001$

Explanatory variables that are associated with an absolute change in QoL (mental and physical) after the intervention
[a] Assessed through R&G Questionnaire

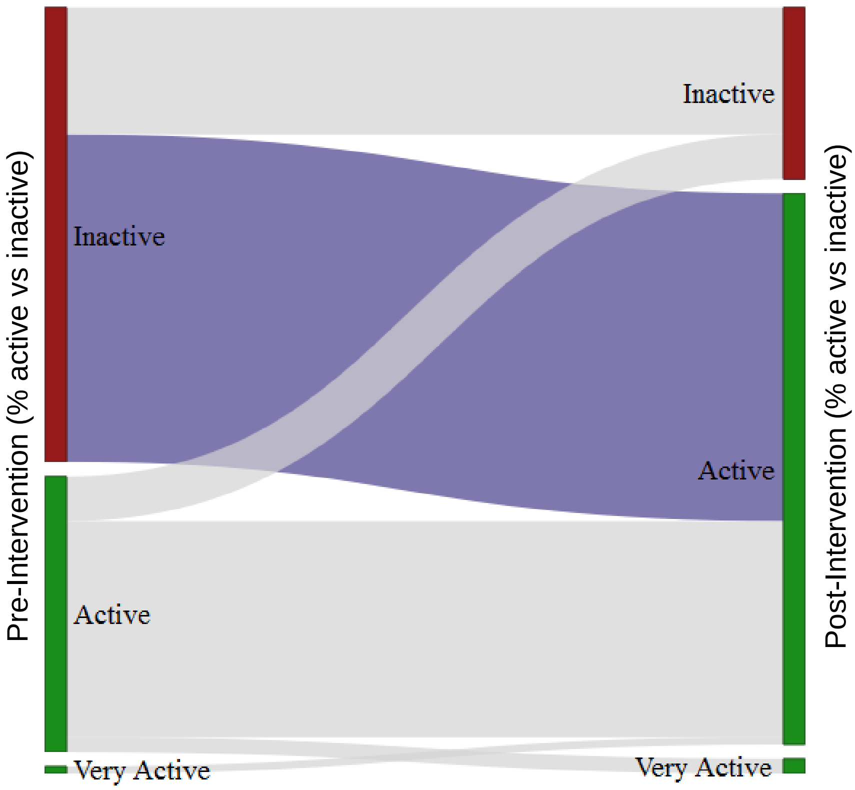


Figure 5. Change in physical activity levels between pre- and post-intervention visits assessed with the R&G questionnaire. The purple link demonstrate patients who improved their physical activity category level from inactive pre-intervention to active post-intervention. The percentage of inactive patients decreased significantly from 67.9% to 34.2%.

3.6 Long-term Effects

For the 103 people that had completed the 12-month visit, a longitudinal analysis was conducted to determine if the outcome variables maintained the initial increase observed after the intervention. The change in VO_2 was not sustained at the 6-month and 12-month post intervention visits when the model was adjusted for age, BMI, sex, activity level and diagnosis (Table 7). The between-person variance was responsible for 71% of variance within the adjusted model and the model explained 41.8% of variance with the fixed effects. The six-minute walk test showed different results with relation to the visits. The number of meters walked was significantly higher even at 12-months post-intervention in both the unadjusted and adjusted models (Table 8). The adjusted model's fixed effects explained 49.7% of the total variance within the model.

In the SF-36, the mental score was not significantly different from baseline at any long-term follow-up. The physical score was significantly different from baseline at all 3 post-intervention time-points in the unadjusted model, but were no longer significantly different when adjusted for PA levels at each time-point, suggesting mediation through PA levels (Table 9). The PA levels were also significantly different from baseline at all time-points after the intervention, with only the number of intervention sessions and BMI as explanatory variables (Table 10). The overall trends for each of the 5 outcome variables are displayed in Figure 6.

Table 7. Unadjusted and adjusted mixed-effects models for explaining changes in VO_2

	Model 1		Model 2	
Fixed Effects	β	p-value	β	p-value
DV: VO_2				
Intercept	22.08	$p < 0.001$	10.22	$p = 0.093$
Post Intervention Visit	1.61	$p < 0.001$	1.25	$p < 0.01$
6 Months Post Intervention Visit	1.11	$p < 0.05$	1.01	$p = 0.053$
12 Months Post Intervention Visit	0.16	$p = 0.69$	- 0.13	$p = 0.75$
Age (Transformed) [a]			0.90	$p < 0.001$
BMI			- 0.32	$p < 0.05$
Sex (ref: female)			5.00	$p < 0.001$
Activity Level (R&G Questionnaire)			0.06	$p < 0.05$
Respiratory Disease (ref: none)			- 7.90	$p < 0.001$
Cardio-metabolic Disease (ref: none)			- 3.27	$p < 0.05$
Random Effects				
σ^2 [b]	7.96		7.59	
τ_{00} Patient [c]	38.28		18.92	
ICC Patient [d]	0.83		0.71	
Marginal R^2 / Conditional R^2 [e]	0.010	0.830	0.418	0.833
AIC [f]	2339.54		2278.35	

Model 1 is unadjusted with only the visit number explaining the change in VO_2. Model 2 is adjusted on other explanatory variables and the R^2 for the fixed effects increases from 0.010 to 0.418. The visits are all compared to the pre-intervention visit; a = Age was transformed using the IMAP equation; b = the within-person variance; c = the between-person variance; d = the intra-class coefficient (ICC), which is the percent of variance explained by between-person variance; e = marginal R^2 is the variance explained by the fixed-effects portion of the model, conditional R^2 is the variance explained by both the fixed and random effects; f = the Akaike Information Criterion, which estimates the quality of the statistical model. A lower number is associated with a better model.

Table 8. Unadjusted and adjusted mixed-effects models for explaining changes in the Six Minute Walk

	Model 1		Model 2	
Fixed Effects	β	p-value	β	p-value
DV: Six Minute Walk Test				
Intercept	528.12	$p < 0.001$	119.25	$p = 0.149$
Post Intervention Visit	29.99	$p < 0.001$	19.58	$p < 0.05$
6 Months Post Intervention Visit	34.13	$p < 0.001$	27.83	$p < 0.01$
12 Months Post Intervention Visit	33.40	$p < 0.001$	25.29	$p < 0.01$
Age (Transformed) [a]			1.00	$p < 0.001$
BMI			- 6.45	$p < 0.001$
Sex (ref: female)			51.64	$p < 0.001$
Activity Level (R&G Questionnaire)			1.72	$p < 0.001$
Respiratory Disease (ref: none)			- 105.41	$p < 0.001$
Depression (ref: none)			54.55	$p < 0.05$
Random Effects				
σ^2 [b]	2716.27		2613.22	
τ_{00} Patient [c]	7224.12		2663.19	
ICC Patient [d]	0.73		0.50	
Marginal R^2 / Conditional R^2 [e]	0.021	0.732	0.497	0.755
AIC [f]	4687.67		4592.09	

Model 1 is unadjusted with only the visit number explaining the change in the six-minute walk test. Model 2 is adjusted on other explanatory variables and the R^2 for the fixed effects increases from 0.021 to 0.497. The visits are all compared to the pre-intervention visit; a = Age was transformed using the IMAP equation; b = the within-person variance; c = the between-person variance; d = the intra-class coefficient (ICC), which is the percent of variance explained by between-person variance; e = marginal R^2 is the variance explained by the fixed-effects portion of the model, conditional R^2 is the variance explained by both the fixed and random effects; f = the Akaike Information Criterion, which estimates the quality of the statistical model. A lower number is associated with a better model.

Table 9. Unadjusted and adjusted mixed-effects models for explaining changes in SF-36 Physical Component

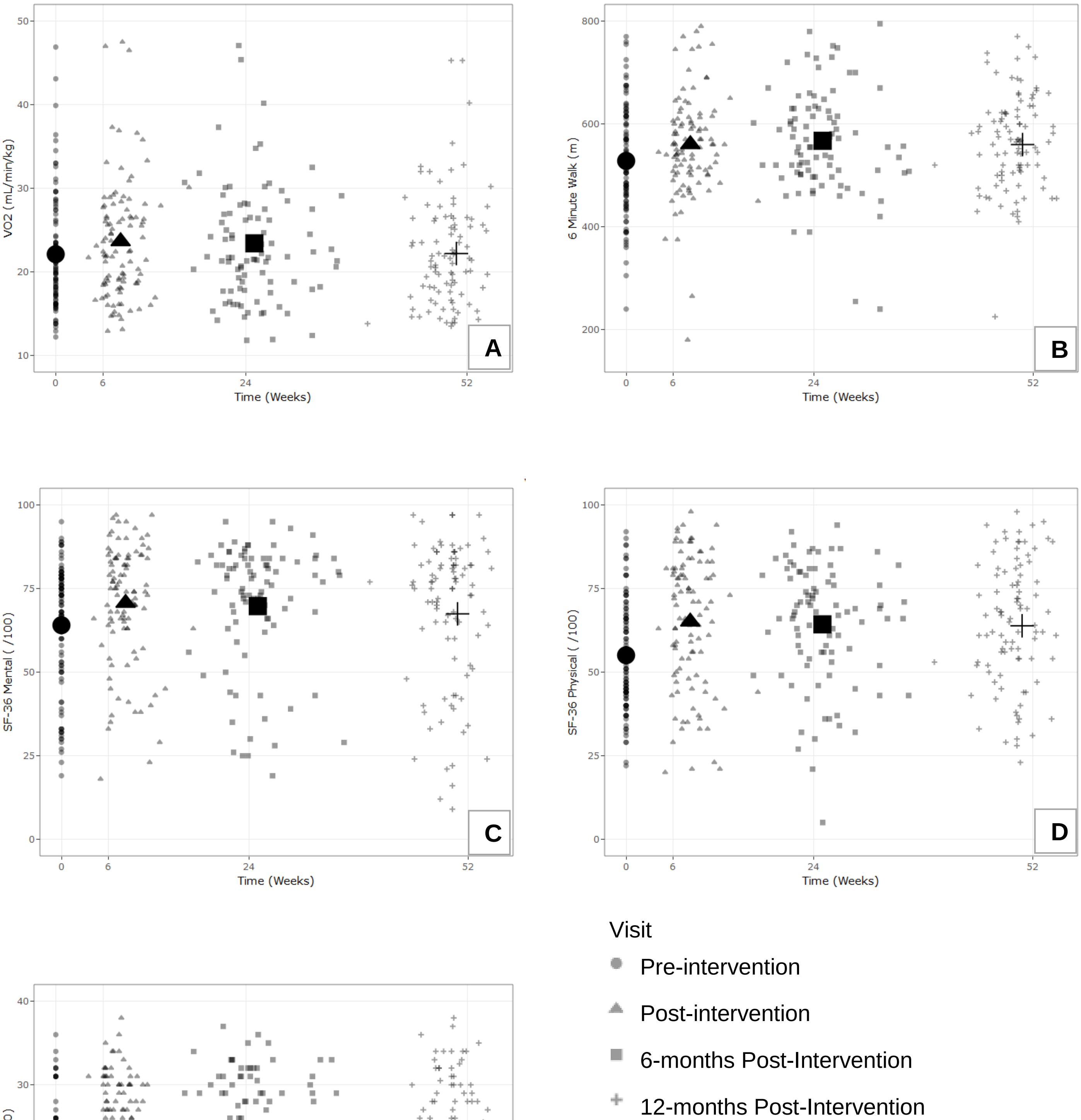
	Model 1		Model 2	
Fixed Effects	β	p-value	β	p-value
DV: SF-36 Physical				
Intercept	57.58	$p < 0.001$	26.59	$p < 0.001$
Post Intervention Visit	7.49	$p < 0.01$	4.36	$p = 0.131$
6 Months Post Intervention Visit	5.61	$p < 0.05$	2.70	$p = 0.424$
12 Months Post Intervention Visit	6.17	$p < 0.01$	3.76	$p = 0.199$
Activity Level (R&G Questionnaire)			0.52	$p < 0.001$
Number of Intervention Sessions			1.46	$p < 0.01$
Random Effects				
$\sigma^{2\ a}$	199.79		206.47	
$\tau_{00\ \text{Patient}}{}^{b}$	121.67		80.00	
ICC $_{\text{Patient}}{}^{c}$	0.38		0.28	
Marginal R^2 / Conditional $R^{2\ d}$	0.028	0.396	0.117	0.363
AIC [e]	3486.79		3471.59	

Model 1 is unadjusted with only the visit number explaining the change in the SF-36 physical component. Model 2 is adjusted on other explanatory variables and the R^2 for the fixed effects increases from 0.028 to 0.117. The visits are all compared to the pre-intervention visit; a = the within-person variance; b = the between-person variance; c = the intra-class coefficient (ICC), which is the percent of variance explained by between-person variance; d = marginal R^2 is the variance explained by the fixed-effects portion of the model, conditional R^2 is the variance explained by both the fixed and random effects; e = the Akaike Information Criterion, which estimates the quality of the statistical model. A lower number is associated with a better model.

Table 10. Unadjusted and adjusted mixed-effects models for explaining changes in Physical Activity Levels

	Model 1		Model 2	
Fixed Effects	β	p-value	β	p-value
DV: R&G Activity Score				
Intercept	17.25	$p < 0.001$	12.00	$p < 0.001$
Post Intervention Visit	6.51	$p < 0.001$	6.37	$p < 0.001$
6 Months Post Intervention Visit	5.07	$p < 0.001$	5.11	$p < 0.001$
12 Months Post Intervention Visit	5.28	$p < 0.001$	5.29	$p < 0.001$
Number of Intervention Sessions			0.73	$p < 0.01$
BMI			- 0.21	$p < 0.05$
Random Effects				
$\sigma^{2\ a}$	45.68		44.95	
$\tau_{00\ \text{Patient}}{}^{b}$	24.43		22.95	
ICC $_{\text{Patient}}{}^{c}$	0.35		0.33	
Marginal R^2 / Conditional $R^{2\ d}$	0.076	0.398	0.109	0.401
AIC [e]	2869.53		2849.57	

Model 1 is unadjusted with only the visit number explaining the change in physical activity levels as assessed by the R&G questionnaire. Model 2 is adjusted on other explanatory variables and the R^2 for the fixed effects increases from 0.076 to 0.109. The visits are all compared to the pre-intervention visit; a = the within-person variance; b = the between-person variance; c = the intra-class coefficient (ICC), which is the percent of variance explained by between-person variance; d = marginal R^2 is the variance explained by the fixed-effects portion of the model, conditional R^2 is the variance explained by both the fixed and random effects; e = the Akaike Information Criterion, which estimates the quality of the statistical model. A lower number is associated with a better model.



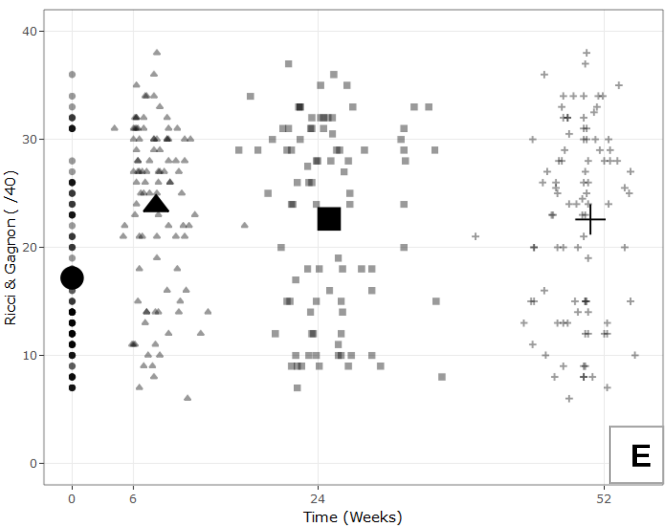


Figure 6. Mean and individual scores at all 4 visits (baseline, post-intervention, 6-months post-intervention, and 12-months post-intervention)
A. VO_2 at all 4 visits;
B. 6 Minute Walk at all 4 visits;
C. SF-36 Mental at all 4 visits;
D. SF-36 Physical at all 4 visits;
E. R&G Score (PA level) at all 4 visits

4. Discussion

4.1 Overall Benefits

The intervention was attributed to a significant initial change in all 5 outcome variables (VO_2, six-minute walk, SF-36 mental, SF-36 physical, and PA levels). PA levels remained significantly higher than baseline levels even one-year post-intervention, demonstrating that this intervention was able to instill a lasting impact on patient's lifestyle. This lasting change in PA levels is crucial for slowing and potentially preventing further disease progression, with previous research demonstrating a decreased progression of coronary artery disease and decreased cardiovascular events with increased PA.[31, 37] Other studies have reported increased CD4 counts in patients with HIV, increased chemotherapy completion rates in breast cancer patients, and an attenuated decline in lung function for those with moderate-to-severe COPD due to increased PA levels.[42, 44, 94]

Benefits of the intervention were also affected by other factors. Those who commenced the intervention with an aerobic capacity, QoL, or PA level below the mean saw a greater increase than those who commenced above the mean. Those with a higher attendance rate during the intervention increased their PA levels by a greater amount, and in turn those with higher PA levels post intervention had a significantly higher physical QoL. Those who took fewer medications also saw a greater change in aerobic capacity and QoL. The total number of medications could be considered a potential proxy for disease severity and comorbidities insinuating that those with less severe conditions have greater improvements.

4.2 Benefits by Diagnosis

For patients with mental disorders and depression, a significantly greater increase was seen through this intervention in the mental QoL scores compared to those with other chronic diseases, with a large increase also present in the physical QoL score. While many studies have researched the link between PA and QoL, less have discussed the link between PA interventions and QoL in these patients. One study found a statistically significant increase in physical QoL, but not in any of the other QoL domains, for women with depression over an 8-week intervention period.[95] Another study with a PA intervention spanning 10 weeks for people with schizophrenia determined that a significant change in the physical and mental domains of QoL occurred post-intervention, which matches the findings of this study.[96] The greater change in this group compared to the others could be due to their significantly lower baseline mental QoL. Another potential explanation for the change in this population could be the group dynamic of this intervention. The 18 sessions were completed as a cohort by the same 6 participants. The inverse relationship between depression and social activities has been widely researched and studies have shown that individuals who participate in social community-based programs see increased QoL. .[97, 98] Future comparison between group and individual PA interventions could further determine the relationship between these variables in this population.

Changes in PA levels were very impressive for all diagnosis groups. However, patients with cancer increased significantly more post-intervention than those without cancer. This finding is specific to our intervention as no previous study has compared the changes in PA levels between various chronic disease diagnoses. One possible explanation for this finding is that in this specific population, patients with cancer were the only group to have a baseline median BMI classified as healthy, and the lowest median total number of medications, suggesting that they began the intervention in an overall healthier physical state then those without cancer. These patients included different types of cancer, different stages of cancer, and different levels of treatment. Those at the end of their treatment course or those with low stage cancer could have less hindering them from improving their PA levels compared to others.

All diagnosis groups followed a similar pattern of change for aerobic capacity, with no significant difference between the trends. However, when a categorical variable that grouped participants as either having a 'very poor' or 'not very poor' VO_2 was included, those with a respiratory diagnosis saw the largest change in the percentage of people that moved from 'very poor' to 'not very poor' VO_2 after the intervention. Initially 70.6% of patients with a respiratory disease were classified as having a 'very poor' VO_2 based on normative data but after the intervention this had decreased significantly to 56.9% of people.[90] This has the potential to be clinically important as those with 'very poor' VO_2 values (the lowest aerobic capacity) have the highest risk for many postoperative complications and mortality. They have also been shown to have worse cognitive processing speed than those with higher VO_2 values.[99, 100]

4.3 PA levels and Physical QoL

It is not surprising that PA levels and physical QoL are significantly correlated and there is undoubtedly an effect of each variable on the other with improved PA levels corresponding to increased QoL and increased QoL leading to a greater increase in PA levels. However, it is likely that the main direction for this relationship is PA levels effecting QoL. Several studies and a systematic reviews have demonstrated the increased benefits to QoL through PA, while also explaining through focus groups that enhanced QoL is one of the motivating factors for people to increase their PA levels.[101-103] The changes in physical QoL in this intervention were shown to be mediated by the PA levels of patients. In the mixed effects regression for SF-36 physical, all post-intervention visits were statistically significant compared to the pre-intervention visit when ‘visit’ was the only explanatory variable. However, when the PA levels were added as a second explanatory variable, no post-intervention visit was significantly different from the pre-intervention visit, implying full mediation through PA levels. Another mixed effects regression with PA levels as the outcome variable was created. Once again, when ‘visit’ was the singular explanatory variable all post-intervention visits were significantly different from the pre-intervention level. Physical QoL was added as a second explanatory variable and, whilst significantly related to PA levels did not negate the significance of the visit variable. This demonstrates only partial mediation and implies, as previous research has shown, that PA levels have a larger effect on QoL than QoL does on PA levels.

4.4 Is a 6-Week Intervention Enough?

There was a lasting impact seen on PA levels throughout all diagnosis groups after only a 6-week PA intervention, and the number of sessions was strongly correlated to the PA levels reported by participants (Table 10). Unlike other studies that did not evaluate the number of intervention sessions attended as an explanatory variable, this was considered highly important by the evaluation team because this intervention was not conducted as a study but as patient’s ‘standard of care’ treatment. Thus, maximizing the benefits of the ongoing intervention with the least effort required from participants and staff was of great importance. When participants were split into quartiles based on session attendance and those in the bottom quartile were compared to the top 3 quartiles, a significant difference between the groups was seen in the PA levels post intervention with those in the bottom quartile having lower scores. However, when the top quartile was compared to the three bottom quartiles, no significant difference in post-intervention PA levels was seen, implying a tapering of the association curve.

However, finding the optimal PA intervention program requires numerous considerations. It is very plausible that duration is not the most important factor, but instead the intensity of the intervention, and the intervention components are what ensure lasting changes to PA levels. Incorporating both aerobic and resistance training allows for greater overall benefits to participants whilst incorporating teaching sessions enables participants to gain an appreciation for the benefits of PA and recommendations for how to incorporate PA into their daily lives. Overall, this is a very feasible PA intervention, with a relatively short duration time.

4.5 Strengths and Limitations

The intervention at Hôtel Dieu incorporates a broad range of patients and tests which allowed for a global assessment on the impact PA has on these patients' lives. Due to the large range of diagnosis groups included in the study, novel comparisons between diagnosis groups were performed. Including this wide range of diagnoses also allows for easier generalizability of the results to the general population as it is often the case that comorbidities exist in people with a chronic disease. This intervention was also conducted as part of patients' standard of care and not as a study. The high level of retention within the intervention and the benefits to PA levels, QoL, and aerobic capacity signify both that PA is important to this population and that it can have lasting effects on patient's lives.

Several limitations existed in this evaluation. The patients lost to follow up differed in their QoL baseline questionnaire in comparison to those who remained. Another limitation was the lack of validation for the R&G questionnaire used to assess PA levels. However, it is a well-used questionnaire in France which allows for comparison between populations. It has also previously been used in conjunction with the IPAQ to an agreeable level.[54] In addition, because this was conducted as patient's standard of care, no control group existed that could be used comparison, but the mixed-effects regression allowed for a strong analysis by taking into account person differences. However, as currently only 103 participants have completed the 12-month visit, no long-term effects have been evaluated by diagnosis. It will be important to evaluate if the differences between groups that were shown immediately post-intervention are still present after both 6 and 12 months.

4.6 Future Considerations

Completing an evaluation of the long-term effects by diagnosis will allow a more in depth understanding of the benefits experienced through the intervention. Whilst conducting a specific analysis for each diagnosis group could allow for better comparisons to other studies that focus on only one diagnosis, while also allowing for more focused conclusions on the effects of medications and treatment within the group. The potential to expand the intervention through tele-communication to those unable to attend the sessions in person due to distance or time should be considered, although the risk of unsupervised exercise in each specific patient would need to be independently assessed.

Moving forward, utilising another PA questionnaire in conjunction with the R&G questionnaire would be useful for confirming validated PA levels in these patients, however even the French version of the self-administered IPAQ has still not been validated. Therefore, patients would need to be capable of speaking another language that has a validated IPAQ in order to establish validated PA levels in a French population through a self-administered questionnaire. Alternatively, validating the widely used R&G questionnaire through objective measures could be considered. This would be a cost-heavy task since objectively measured PA devices are relatively costly.

The social aspects of the intervention, especially for patients with mental disorders could be examined through an assessment of their social QoL. This could be conducted through the completion of the WHOQOL-Bref questionnaire, which has established norms for the French population in physical health, psychological health, and social relationship dimensions.[104]

An additional analysis that should be considered in the future is an economic analysis of this program. Quality adjusted life years (QALYs) could be generated through the SF-36 questionnaire using the SF-6D in order to perform a cost utility analysis.[105] Cost information could be retrieved through insurances databases and the Hospinnomics department at Hôtel Dieu to ensure that this intervention is financially cost-effective in addition to the individual health and fitness benefits received by participants.

5. Conclusion

This evaluation demonstrates the many benefits of a PA intervention for a wide range of chronic diseases. There is a significant reduction in the number of patients who are classified as inactive after the intervention from 67.9% to 34.2%. This change is still significant 12 months after the intervention and, in turn, is associated with positive long-term physical QoL changes. These improvements to QoL are greatest in those with mental disorders. VO_2 levels are greatly improved with significantly fewer people classified as having 'very poor' VO_2 after the intervention, especially in those with respiratory disease. This is complemented by a significant lasting change in the distance walked over six minutes, even 12 months after the intervention. PA should be highly considered as a form of treatment for these patients, especially those with low initial PA. In addition, PA should be strongly recommended by healthcare professionals in order for these patients to benefit from the demonstrated advantages in aerobic capacity, QoL, and reduction in disease progression. These findings highlight the benefits of simple PA interventions on many different chronic diseases. Future research should continue to focus on intervention types like this that target a wide range of patients, are accessible to many, and are able to be completed with lasting results.

6. References

1. Shephard RJ, Lankenau B, Pratt M, Neiman A, Puska P, Benaziza H, et al. Physical Activity Policy Development: a synopsis of the WHO/CDC Consultation, September 29 through October 2, 2002, Atlanta, Georgia. Public Health Rep. 2004;119(3):346-51. doi: 10.1016/j.phr.2004.04.013. PubMed PMID: 15158113; PubMed Central PMCID: PMCPMC1497637.
2. Duncan MJ, Badland HM, Mummery WK. Applying GPS to enhance understanding of transport-related physical activity. J Sci Med Sport. 2009;12(5):549-56. doi: 10.1016/j.jsams.2008.10.010. PubMed PMID: 19237315.
3. Monda KL, Gordon-Larsen P, Stevens J, Popkin BM. China's transition: the effect of rapid urbanization on adult occupational physical activity. Soc Sci Med. 2007;64(4):858-70. doi: 10.1016/j.socscimed.2006.10.019. PubMed PMID: 17125897; PubMed Central PMCID: PMCPMC2753984.
4. Church TS, Thomas DM, Tudor-Locke C, Katzmarzyk PT, Earnest CP, Rodarte RQ, et al. Trends over 5 decades in U.S. occupation-related physical activity and their associations with obesity. PLoS One. 2011;6(5):e19657. doi: 10.1371/journal.pone.0019657. PubMed PMID: 21647427; PubMed Central PMCID: PMCPMC3102055.
5. Knuth AG, Hallal PC. Temporal trends in physical activity: a systematic review. J Phys Act Health. 2009;6(5):548-59. PubMed PMID: 19953831.
6. France SP. SYNTHÈSE POUR LES PROFESSIONNELS DES RECOMMANDATIONS DE L'ANSES DE FÉVRIER 2016 SUR L'ACTIVITÉ PHYSIQUE ET LA SÉDENTARITÉ. Paris: 2017.
7. Vuillemin A, Escalon H, Bossard C. Activité physique et sédentarité. Saint Denis: Institut national de prévention et d'éducation pour la santé, 2008.
8. Bull FC, Armstrong T, Dixon T, Ham S, Neiman A, Pratt M. Physical Acitivty. Geneva: World Health Organization, 2005.
9. Bull FC, Pratt M, Shephard RJ, Lankenau B. Implementing national population-based action on physical activity--challenges for action and opportunities for international collaboration. Promot Educ. 2006;13(2):127-32. PubMed PMID: 17017290.
10. Barth N, Hupin D, Roche F, Celarier T, Bongue B. La prescription de l'activité physique adaptée chez le sujet âgé : de l'intention à la réalité. Neurologie - Psychiatrie - Gériatrie. 2018;18(105):155-61.
11. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT, et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet. 2012;380(9838):219-29. doi: 10.1016/S0140-6736(12)61031-9. PubMed PMID: 22818936; PubMed Central PMCID: PMCPMC3645500.
12. Duncan MJ, Vandelanotte C, Caperchione C, Hanley C, Mummery WK. Temporal trends in and relationships between screen time, physical activity, overweight and obesity. BMC Public Health. 2012;12:1060. doi: 10.1186/1471-2458-12-1060. PubMed PMID: 23216917; PubMed Central PMCID: PMCPMC3541208.
13. Ng SW, Popkin BM. Time use and physical activity: a shift away from movement across the globe. Obes Rev. 2012;13(8):659-80. doi: 10.1111/j.1467-789X.2011.00982.x. PubMed PMID: 22694051; PubMed Central PMCID: PMCPMC3401184.
14. Vandelanotte C, Sugiyama T, Gardiner P, Owen N. Associations of leisure-time internet and computer use with overweight and obesity, physical activity and sedentary behaviors: cross-sectional study. J Med Internet Res. 2009;11(3):e28. doi: 10.2196/jmir.1084. PubMed PMID: 19666455; PubMed Central PMCID: PMCPMC2762849.
15. Palacios-Cena D, Alonso-Blanco C, Jimenez-Garcia R, Hernandez-Barrera V, Carrasco-Garrido P, Pileno-Martinez E, et al. Time trends in leisure time physical activity and physical fitness in elderly people: 20 year follow-up of the Spanish population national health survey (1987-2006). BMC Public Health. 2011;11:799. doi: 10.1186/1471-2458-11-799. PubMed PMID: 21995560; PubMed Central PMCID: PMCPMC3206481.
16. Stamatakis E, Chaudhury M. Temporal trends in adults' sports participation patterns in England between 1997 and 2006: the Health Survey for England. Br J Sports Med. 2008;42(11):901-8. doi: 10.1136/bjsm.2008.048082. PubMed PMID: 18658250.
17. Organization WH. The world health report 2002: reducing risks, promoting healthy life. Geneva: 2002.
18. Global Burden of Disease Study C. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;386(9995):743-800.

doi: 10.1016/S0140-6736(15)60692-4. PubMed PMID: 26063472; PubMed Central PMCID: PMCPMC4561509.
19. Rook A. An investigation into the longevity of Cambridge sportsmen. Br Med J. 1954;1(4865):773-7. PubMed PMID: 13140858; PubMed Central PMCID: PMCPMC2084826.
20. Blair SN, Davey Smith G, Lee IM, Fox K, Hillsdon M, McKeown RE, et al. A tribute to Professor Jeremiah Morris: the man who invented the field of physical activity epidemiology. Ann Epidemiol. 2010;20(9):651-60. doi: 10.1016/j.annepidem.2010.06.001. PubMed PMID: 20696405.
21. Ashe MC, Miller WC, Eng JJ, Noreau L, Physical A, Chronic Conditions Research T. Older adults, chronic disease and leisure-time physical activity. Gerontology. 2009;55(1):64-72. doi: 10.1159/000141518. PubMed PMID: 18566534; PubMed Central PMCID: PMCPMC3167824.
22. Barker J, Smith Byrne K, Doherty A, Foster C, Rahimi K, Ramakrishnan R, et al. Physical activity of UK adults with chronic disease: cross-sectional analysis of accelerometer-measured physical activity in 96 706 UK Biobank participants. Int J Epidemiol. 2019. doi: 10.1093/ije/dyy294. PubMed PMID: 30721947.
23. Avery L, Flynn D, van Wersch A, Sniehotta FF, Trenell MI. Changing physical activity behavior in type 2 diabetes: a systematic review and meta-analysis of behavioral interventions. Diabetes Care. 2012;35(12):2681-9. doi: 10.2337/dc11-2452. PubMed PMID: 23173137; PubMed Central PMCID: PMCPMC3507564.
24. Dibben GO, Dalal HM, Taylor RS, Doherty P, Tang LH, Hillsdon M. Cardiac rehabilitation and physical activity: systematic review and meta-analysis. Heart. 2018;104(17):1394-402. doi: 10.1136/heartjnl-2017-312832. PubMed PMID: 29654095; PubMed Central PMCID: PMCPMC6109237.
25. Mantoani LC, Rubio N, McKinstry B, MacNee W, Rabinovich RA. Interventions to modify physical activity in patients with COPD: a systematic review. Eur Respir J. 2016;48(1):69-81. doi: 10.1183/13993003.01744-2015. PubMed PMID: 27103381.
26. O'Brien KK, Tynan AM, Nixon SA, Glazier RH. Effectiveness of aerobic exercise for adults living with HIV: systematic review and meta-analysis using the Cochrane Collaboration protocol. BMC Infect Dis. 2016;16:182. doi: 10.1186/s12879-016-1478-2. PubMed PMID: 27112335; PubMed Central PMCID: PMCPMC4845358.
27. Swartz MC, Lewis ZH, Lyons EJ, Jennings K, Middleton A, Deer RR, et al. Effect of Home- and Community-Based Physical Activity Interventions on Physical Function Among Cancer Survivors: A Systematic Review and Meta-Analysis. Arch Phys Med Rehabil. 2017;98(8):1652-65. doi: 10.1016/j.apmr.2017.03.017. PubMed PMID: 28427925; PubMed Central PMCID: PMCPMC5534187.
28. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. CMAJ. 2006;174(6):801-9. doi: 10.1503/cmaj.051351. PubMed PMID: 16534088; PubMed Central PMCID: PMCPMC1402378.
29. Larson JL, Covey MK, Kapella MC, Alex CG, McAuley E. Self-efficacy enhancing intervention increases light physical activity in people with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2014;9:1081-90. doi: 10.2147/COPD.S66846. PubMed PMID: 25336939; PubMed Central PMCID: PMCPMC4199844.
30. Rogers LQ, Courneya KS, Anton PM, Hopkins-Price P, Verhulst S, Vicari SK, et al. Effects of the BEAT Cancer physical activity behavior change intervention on physical activity, aerobic fitness, and quality of life in breast cancer survivors: a multicenter randomized controlled trial. Breast Cancer Res Treat. 2015;149(1):109-19. doi: 10.1007/s10549-014-3216-z. PubMed PMID: 25417174; PubMed Central PMCID: PMCPMC4435784.
31. Arija V, Villalobos F, Pedret R, Vinuesa A, Timon M, Basora T, et al. Effectiveness of a physical activity program on cardiovascular disease risk in adult primary health-care users: the "Pas-a-Pas" community intervention trial. BMC Public Health. 2017;17(1):576. doi: 10.1186/s12889-017-4485-3. PubMed PMID: 28619115; PubMed Central PMCID: PMCPMC5471891.
32. Stoa EM, Meling S, Nyhus LK, Glenn S, Mangerud KM, Helgerud J, et al. High-intensity aerobic interval training improves aerobic fitness and HbA1c among persons diagnosed with type 2 diabetes. Eur J Appl Physiol. 2017;117(3):455-67. doi: 10.1007/s00421-017-3540-1. PubMed PMID: 28160083.
33. Coultas DB, Jackson BE, Russo R, Peoples J, Sloan J, Singh KP, et al. A Lifestyle Physical Activity Intervention for Patients with Chronic Obstructive Pulmonary Disease. A Randomized Controlled Trial. Ann Am Thorac Soc. 2016;13(5):617-26. doi: 10.1513/AnnalsATS.201508-508OC. PubMed PMID: 26785249; PubMed Central PMCID: PMCPMC5018892.
34. Dieli-Conwright CM, Courneya KS, Demark-Wahnefried W, Sami N, Lee K, Sweeney FC, et al. Aerobic and resistance exercise improves physical fitness, bone health, and quality of life in overweight and obese breast cancer survivors: a randomized controlled trial. Breast Cancer Res.

2018;20(1):124. doi: 10.1186/s13058-018-1051-6. PubMed PMID: 30340503; PubMed Central PMCID: PMCPMC6194749.
35. Gomes Neto M, Conceicao CS, Oliveira Carvalho V, Brites C. Effects of Combined Aerobic and Resistance Exercise on Exercise Capacity, Muscle Strength and Quality of Life in HIV-Infected Patients: A Systematic Review and Meta-Analysis. PLoS One. 2015;10(9):e0138066. doi: 10.1371/journal.pone.0138066. PubMed PMID: 26378794; PubMed Central PMCID: PMCPMC4574781.
36. Rosenbaum S, Tiedemann A, Sherrington C, Curtis J, Ward PB. Physical activity interventions for people with mental illness: a systematic review and meta-analysis. J Clin Psychiatry. 2014;75(9):964-74. doi: 10.4088/JCP.13r08765. PubMed PMID: 24813261.
37. Taylor RS, Brown A, Ebrahim S, Jolliffe J, Noorani H, Rees K, et al. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. Am J Med. 2004;116(10):682-92. doi: 10.1016/j.amjmed.2004.01.009. PubMed PMID: 15121495.
38. Adamsen L, Midtgaard J, Rorth M, Borregaard N, Andersen C, Quist M, et al. Feasibility, physical capacity, and health benefits of a multidimensional exercise program for cancer patients undergoing chemotherapy. Support Care Cancer. 2003;11(11):707-16. doi: 10.1007/s00520-003-0504-2. PubMed PMID: 12898370.
39. Galvao DA, Newton RU. Review of exercise intervention studies in cancer patients. J Clin Oncol. 2005;23(4):899-909. doi: 10.1200/JCO.2005.06.085. PubMed PMID: 15681536.
40. Sweegers MG, Altenburg TM, Chinapaw MJ, Kalter J, Verdonck-de Leeuw IM, Courneya KS, et al. Which exercise prescriptions improve quality of life and physical function in patients with cancer during and following treatment? A systematic review and meta-analysis of randomised controlled trials. Br J Sports Med. 2018;52(8):505-13. doi: 10.1136/bjsports-2017-097891. PubMed PMID: 28954800.
41. Esteban C, Quintana JM, Aburto M, Moraza J, Egurrola M, Perez-Izquierdo J, et al. Impact of changes in physical activity on health-related quality of life among patients with COPD. Eur Respir J. 2010;36(2):292-300. doi: 10.1183/09031936.00021409. PubMed PMID: 20075059.
42. Courneya KS, Segal RJ, Mackey JR, Gelmon K, Reid RD, Friedenreich CM, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. J Clin Oncol. 2007;25(28):4396-404. doi: 10.1200/JCO.2006.08.2024. PubMed PMID: 17785708.
43. Dunstan DW, Daly RM, Owen N, Jolley D, Vulikh E, Shaw J, et al. Home-based resistance training is not sufficient to maintain improved glycemic control following supervised training in older individuals with type 2 diabetes. Diabetes Care. 2005;28(1):3-9. PubMed PMID: 15616225.
44. Ogalha C, Luz E, Sampaio E, Souza R, Zarife A, Neto MG, et al. A randomized, clinical trial to evaluate the impact of regular physical activity on the quality of life, body morphology and metabolic parameters of patients with AIDS in Salvador, Brazil. J Acquir Immune Defic Syndr. 2011;57 Suppl 3:S179-85. doi: 10.1097/QAI.0b013e31821e9bca. PubMed PMID: 21857315.
45. Waschki B, Kirsten AM, Holz O, Mueller KC, Schaper M, Sack AL, et al. Disease Progression and Changes in Physical Activity in Patients with Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2015;192(3):295-306. doi: 10.1164/rccm.201501-0081OC. PubMed PMID: 26020495.
46. Gonzalez-Gross M, Melendez A. Sedentarism, active lifestyle and sport: Impact on health and obesity prevention. Nutr Hosp. 2013;28 Suppl 5:89-98. doi: 10.3305/nh.2013.28.sup5.6923. PubMed PMID: 24010748.
47. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-83. PubMed PMID: 1593914.
48. McHorney CA, Ware JE, Jr., Rogers W, Raczek AE, Lu JF. The validity and relative precision of MOS short- and long-form health status scales and Dartmouth COOP charts. Results from the Medical Outcomes Study. Med Care. 1992;30(5 Suppl):MS253-65. PubMed PMID: 1583937.
49. Lins L, Carvalho FM. SF-36 total score as a single measure of health-related quality of life: Scoping review. SAGE Open Med. 2016;4:2050312116671725. doi: 10.1177/2050312116671725. PubMed PMID: 27757230; PubMed Central PMCID: PMCPMC5052926.
50. Ware JE, Jr., Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. J Clin Epidemiol. 1998;51(11):903-12. PubMed PMID: 9817107.
51. Brazier JE, Harper R, Jones NM, O'Cathain A, Thomas KJ, Usherwood T, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. BMJ. 1992;305(6846):160-4. PubMed PMID: 1285753; PubMed Central PMCID: PMCPMC1883187.
52. Limsuwat C, McClellan R, Amiri HM, Nugent K. Pulmonary rehabilitation improves only some domains of health-related quality of life measured by the Short Form-36 questionnaire. Ann Thorac

Med. 2014;9(3):144-8. doi: 10.4103/1817-1737.134068. PubMed PMID: 24987472; PubMed Central PMCID: PMCPMC4073570.
53. D'après J. Ricci et L. Gagnon, université de Montréal, modifié par F. Laureyns et JM. Séné.
54. Duclos M, Dejager S, Postel-Vinay N, di Nicola S, Quere S, Fiquet B. Physical activity in patients with type 2 diabetes and hypertension--insights into motivations and barriers from the MOBILE study. Vasc Health Risk Manag. 2015;11:361-71. doi: 10.2147/VHRM.S84832. PubMed PMID: 26170686; PubMed Central PMCID: PMCPMC4492639.
55. Haroutel D, F A, Boucherot V, Deliot G, Trichot S, Boyer F. Physical and rehabilitation medicine and health sport network in Champagne Region: A descriptive study over 1 year. Annals of Physical Rehabilitation Medicine. 2016;56(Supplement):e55.
56. Reichhart K, Evesque M, Cavana M, Msuzynski P, Leclercq M, Winisdoerffer N, et al. How to promote physical activity maintenance after an exercise-training program in cancer patients? Annals of Physical Rehabilitation Medicine. 2016;59(Supplement):e55.
57. Berthelot G, Bar-Hen A, Marck A, Foulonneau V, Douady S, Noirez P, et al. An integrative modeling approach to the age-performance relationship in mammals at the cellular scale. Sci Rep. 2019;9(1):418. doi: 10.1038/s41598-018-36707-3. PubMed PMID: 30674921; PubMed Central PMCID: PMCPMC6344496.
58. Netuveli G, Wiggins RD, Hildon Z, Montgomery SM, Blane D. Quality of life at older ages: evidence from the English longitudinal study of aging (wave 1). J Epidemiol Community Health. 2006;60(4):357-63. doi: 10.1136/jech.2005.040071. PubMed PMID: 16537355; PubMed Central PMCID: PMCPMC2566174.
59. Takagi D, Nishida Y, Fujita D. Age-associated changes in the level of physical activity in elderly adults. J Phys Ther Sci. 2015;27(12):3685-7. doi: 10.1589/jpts.27.3685. PubMed PMID: 26834332; PubMed Central PMCID: PMCPMC4713771.
60. Azevedo MR, Araujo CL, Reichert FF, Siqueira FV, da Silva MC, Hallal PC. Gender differences in leisure-time physical activity. Int J Public Health. 2007;52(1):8-15. PubMed PMID: 17966815; PubMed Central PMCID: PMCPMC2778720.
61. Campos AC, Ferreira e Ferreira E, Vargas AM, Albala C. Aging, Gender and Quality of Life (AGEQOL) study: factors associated with good quality of life in older Brazilian community-dwelling adults. Health Qual Life Outcomes. 2014;12:166. doi: 10.1186/s12955-014-0166-4. PubMed PMID: 25433521; PubMed Central PMCID: PMCPMC4261579.
62. Riedinger MS, Dracup KA, Brecht ML, Padilla G, Sarna L, Ganz PA. Quality of life in patients with heart failure: do gender differences exist? Heart Lung. 2001;30(2):105-16. PubMed PMID: 11248713.
63. Radovanovic S, Kocic S, Gajovic G, Radevic S, Milosavljevic M, Niciforovic J. The impact of body weight on aerobic capacity. Med Glas (Zenica). 2014;11(1):204-9. PubMed PMID: 24496365.
64. Bottone FG, Jr., Hawkins K, Musich S, Cheng Y, Ozminkowski RJ, Migliori RJ, et al. The relationship between body mass index and quality of life in community-living older adults living in the United States. J Nutr Health Aging. 2013;17(6):495-501. doi: 10.1007/s12603-013-0022-y. PubMed PMID: 23732544.
65. Organization WH. International statistical classification of diseases and related health problems, 10th revision, Fifth edition, 2016. Geneva: WHO, 2015.
66. Gasparini. Comorbidity: An R package for computing comorbidity scores. Journal of Open Source Software. 2018;3(23):648. doi: https://doi.org/10.21105/joss.00648.
67. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005;43(11):1130-9. PubMed PMID: 16224307.
68. Dominick KL, Dudley TK, Coffman CJ, Bosworth HB. Comparison of three comorbidity measures for predicting health service use in patients with osteoarthritis. Arthritis Rheum. 2005;53(5):666-72. doi: 10.1002/art.21440. PubMed PMID: 16208675.
69. Quail JM, Lix LM, Osman BA, Teare GF. Comparing comorbidity measures for predicting mortality and hospitalization in three population-based cohorts. BMC Health Serv Res. 2011;11:146. doi: 10.1186/1472-6963-11-146. PubMed PMID: 21663672; PubMed Central PMCID: PMCPMC3127985.
70. Southern DA, Quan H, Ghali WA. Comparison of the Elixhauser and Charlson/Deyo methods of comorbidity measurement in administrative data. Med Care. 2004;42(4):355-60. PubMed PMID: 15076812.
71. Moore BJ, White S, Washington R, Coenen N, Elixhauser A. Identifying Increased Risk of Readmission and In-hospital Mortality Using Hospital Administrative Data: The AHRQ Elixhauser

Comorbidity Index. Med Care. 2017;55(7):698-705. doi: 10.1097/MLR.0000000000000735. PubMed PMID: 28498196.
72. van Walraven C, Austin PC, Jennings A, Quan H, Forster AJ. A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data. Med Care. 2009;47(6):626-33. doi: 10.1097/MLR.0b013e31819432e5. PubMed PMID: 19433995.
73. Guidelines for ATC classification and DDD assignment 2019 [Internet]. Oslo, Norway; 2018
74. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr. 2017;17(1):230. doi: 10.1186/s12877-017-0621-2. PubMed PMID: 29017448; PubMed Central PMCID: PMCPMC5635569.
75. Montiel-Luque A, Nunez-Montenegro AJ, Martin-Aurioles E, Canca-Sanchez JC, Toro-Toro MC, Gonzalez-Correa JA, et al. Medication-related factors associated with health-related quality of life in patients older than 65 years with polypharmacy. PLoS One. 2017;12(2):e0171320. doi: 10.1371/journal.pone.0171320. PubMed PMID: 28166266; PubMed Central PMCID: PMCPMC5293190.
76. Clarke C, Witham M. The Effects of Medication on Activity and Rehabilitation of Older People – Opportunities and Risks. Rehabilitation Process and Outcome. 2017;6.
77. Marti B, Abelin T, Minder CE, Vader JP. Smoking, alcohol consumption, and endurance capacity: an analysis of 6,500 19-year-old conscripts and 4,100 joggers. Prev Med. 1988;17(1):79-92. PubMed PMID: 3258987.
78. LaCroix AZ, Guralnik JM, Berkman LF, Wallace RB, Satterfield S. Maintaining mobility in late life. II. Smoking, alcohol consumption, physical activity, and body mass index. Am J Epidemiol. 1993;137(8):858-69. PubMed PMID: 8484377.
79. Garces YI, Yang P, Parkinson J, Zhao X, Wampfler JA, Ebbert JO, et al. The relationship between cigarette smoking and quality of life after lung cancer diagnosis. Chest. 2004;126(6):1733-41. doi: 10.1378/chest.126.6.1733. PubMed PMID: 15596667.
80. Crothers K, Griffith TA, McGinnis KA, Rodriguez-Barradas MC, Leaf DA, Weissman S, et al. The impact of cigarette smoking on mortality, quality of life, and comorbid illness among HIV-positive veterans. J Gen Intern Med. 2005;20(12):1142-5. doi: 10.1111/j.1525-1497.2005.0255.x. PubMed PMID: 16423106; PubMed Central PMCID: PMCPMC1490270.
81. Sippel JM, Pedula KL, Vollmer WM, Buist AS, Osborne ML. Associations of smoking with hospital-based care and quality of life in patients with obstructive airway disease. Chest. 1999;115(3):691-6. PubMed PMID: 10084477.
82. Volk RJ, Cantor SB, Steinbauer JR, Cass AR. Alcohol use disorders, consumption patterns, and health-related quality of life of primary care patients. Alcohol Clin Exp Res. 1997;21(5):899-905. PubMed PMID: 9267541.
83. Skevington SM. Qualities of life, educational level and human development: an international investigation of health. Soc Psychiatry Psychiatr Epidemiol. 2010;45(10):999-1009. doi: 10.1007/s00127-009-0138-x. PubMed PMID: 19820887.
84. Gray PM, Murphy MH, Gallagher AM, Simpson EE. Motives and Barriers to Physical Activity Among Older Adults of Different Socioeconomic Status. J Aging Phys Act. 2016;24(3):419-29. doi: 10.1123/japa.2015-0045. PubMed PMID: 26671896.
85. Team RC. R: A language and environment for statsical computing. . Vienna, Austria: R Foundation for Statistical Computing, 2018.
86. Scheffer J. Dealing With Missing Data. Res Lett Inf Math Sci. 2002;3:153-60.
87. Van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. Journal of Statistical Software. 2011;45(3):1-67.
88. Briggs A, Clark T, Wolstenholme J, Clarke P. Missing... presumed at random: cost-analysis of incomplete data. Health Econ. 2003;12(5):377-92. doi: 10.1002/hec.766. PubMed PMID: 12720255.
89. Lumley T. mitools: Tools for Multiple Imputation of Missing Data. 2019.
90. Shvartz E, Reibold RC. Aerobic fitness norms for males and females aged 6 to 75 years: a review. Aviat Space Environ Med. 1990;61(1):3-11. PubMed PMID: 2405832.
91. Gustavson K, von Soest T, Karevold E, Roysamb E. Attrition and generalizability in longitudinal studies: findings from a 15-year population-based study and a Monte Carlo simulation study. BMC Public Health. 2012;12:918. doi: 10.1186/1471-2458-12-918. PubMed PMID: 23107281; PubMed Central PMCID: PMCPMC3503744.
92. Abshire M, Dinglas VD, Cajita MI, Eakin MN, Needham DM, Himmelfarb CD. Participant retention practices in longitudinal clinical research studies with high retention rates. BMC Med Res Methodol. 2017;17(1):30. doi: 10.1186/s12874-017-0310-z. PubMed PMID: 28219336; PubMed Central PMCID: PMCPMC5319074.

93. Gelman AC, JB, Stern H, Rubin D. Bayesian Data Analysis. 2 ed: Chapman & Hall/CRC; 2008.
94. Demeyer H, Donaire-Gonzalez D, Gimeno-Santos E, Ramon MA, J DEB, Benet M, et al. Physical Activity Is Associated with Attenuated Disease Progression in Chronic Obstructive Pulmonary Disease. Med Sci Sports Exerc. 2019;51(5):833-40. doi: 10.1249/MSS.0000000000001859. PubMed PMID: 30531289.
95. Carta MG, Hardoy MC, Pilu A, Sorba M, Floris AL, Mannu FA, et al. Improving physical quality of life with group physical activity in the adjunctive treatment of major depressive disorder. Clin Pract Epidemiol Ment Health. 2008;4:1. doi: 10.1186/1745-0179-4-1. PubMed PMID: 18221549; PubMed Central PMCID: PMCPMC2266746.
96. Acil AA, Dogan S, Dogan O. The effects of physical exercises to mental state and quality of life in patients with schizophrenia. J Psychiatr Ment Health Nurs. 2008;15(10):808-15. doi: 10.1111/j.1365-2850.2008.01317.x. PubMed PMID: 19012672.
97. Petryshen PM, Hawkins JD, Fronchak TA. An evaluation of the social recreation component of a community mental health program. Psychiatr Rehabil J. 2001;24(3):293-8. PubMed PMID: 11315215.
98. Holtfreter K, Reisig MD, Turanovic JJ. Depression and infrequent participation in social activities among older adults: the moderating role of high-quality familial ties. Aging Ment Health. 2017;21(4):379-88. doi: 10.1080/13607863.2015.1099036. PubMed PMID: 26471453.
99. Shafiek H, Valera JL, Togores B, Torrecilla JA, Sauleda J, Cosio BG. Risk of postoperative complications in chronic obstructive lung diseases patients considered fit for lung cancer surgery: beyond oxygen consumption. Eur J Cardiothorac Surg. 2016;50(4):772-9. doi: 10.1093/ejcts/ezw104. PubMed PMID: 27059429.
100. Etnier J, Johnston R, Dagenbach D, Pollard RJ, Rejeski WJ, Berry M. The relationships among pulmonary function, aerobic fitness, and cognitive functioning in older COPD patients. Chest. 1999;116(4):953-60. PubMed PMID: 10531159.
101. Gillison FB, Skevington SM, Sato A, Standage M, Evangelidou S. The effects of exercise interventions on quality of life in clinical and healthy populations; a meta-analysis. Soc Sci Med. 2009;68(9):1700-10. doi: 10.1016/j.socscimed.2009.02.028. PubMed PMID: 19297065.
102. Gill DL, Hammond CC, Reifsteck EJ, Jehu CM, Williams RA, Adams MM, et al. Physical activity and quality of life. J Prev Med Public Health. 2013;46 Suppl 1:S28-34. doi: 10.3961/jpmph.2013.46.S.S28. PubMed PMID: 23412703; PubMed Central PMCID: PMCPMC3567315.
103. Bize R, Johnson JA, Plotnikoff RC. Physical activity level and health-related quality of life in the general adult population: a systematic review. Prev Med. 2007;45(6):401-15. doi: 10.1016/j.ypmed.2007.07.017. PubMed PMID: 17707498.
104. Baumann C, Erpelding ML, Regat S, Collin JF, Briancon S. The WHOQOL-BREF questionnaire: French adult population norms for the physical health, psychological health and social relationship dimensions. Rev Epidemiol Sante Publique. 2010;58(1):33-9. doi: 10.1016/j.respe.2009.10.009. PubMed PMID: 20096515.
105. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ. 2002;21(2):271-92. PubMed PMID: 11939242.

Appendix 1 – Sheffield Ethics

1.1 Declaration Form

Department of Economics/ScHARR

Research Ethics Review
for Undergraduate and Postgraduate-Taught Students

Form 1C: Student Declaration

To be included in Appendices of dissertation

Research Project Title:

Evaluation of a 6-week physical activity intervention for chronic disease patients

Name of dataset to be used:
Intervention Data

Owner of dataset:
Assistance Publique Hôpitaux de Paris

Total number of datasets to be used: 1
If more than one, then fill in a separate declaration for each dataset.

State the case that applies to your research project: Case 2

Case 1: Your proposed project will only involve anonymised/aggregated data that any member of the public is legitimately free to access and use without having to obtain permission from anyone else. E.g., macroeconomic statistics provided by legitimate sources such as government departments and international organisations; anonymised secondary data on individuals or firms provided by legitimate sources such as government departments and which do not require any form of registration or statement of purpose to allow access.

Case 2: Your proposed project will involve anonymised secondary data for which you need to obtain permission from the owner (e.g., you need to satisfy some condition before being permitted to download the data, such as a declaration of intended educational purpose. Downloading the BHPS from the Data Archive falls in this category.)

Case 3: None of the above cases. Note that the department does not allow undergraduate or postgraduate taught students to use primary data, or secondary data that may include personal data, unless specific training is undertaken by the student.

→ If your proposed project falls within Case 1, then simply print your name, date and sign below.
If your proposed project falls within Case 2, then you need to append to this form evidence that you have legitimately obtained access to these data. E.g., confirmation email, and statement of purpose if one was required. Then print your name, date and sign below.
If your proposed project falls within Case 3, then contact your supervisor or supervisory team as soon as possible. You may not be able to use the proposed data.

→ **Name of student:** **Stephanie Duncombe**

→ **Signature of student:** **Date:** 25 Feb 2019

→ **Name of supervisor:** **Pr. Jean-François Toussaint**

→ **Signature of Supervisor:** **Date:** 26 feb 2019

1.2 Permission to Use Data

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CONFIDENTIALITE

Je soussigné, Pr Jean-François Toussaint, Directeur de l'IRMES à l'INSEP 11 avenue du Tremblay – 75012 Paris et Directeur du CIMS, Hôtel-Dieu, AP-HP autorise Melle Stéphanie Duncombe à consulter et utiliser les données scientifiques de l'Institut et du CIMS pour son étude : « *Evalution of a 6-week physical activity intervention for chronic disease patients* »

Ces données sont anonymes.

Tous les sujets concernés ont consenti à voir leurs données analysées statistiquement.

Si une personne venait à s'opposer par la suite à l'utilisation des données qui la concernent, Stéphanie Duncombe s'engage à ne pas les utiliser.

Pr Jean-François TOUSSAINT

1.3 Patient Retrospective Data Consent

HÔPITAUX UNIVERSITAIRES
PARIS CENTRE
Cochin • Port-Royal • Tarnier • Broca
La Collégiale • La Rochefoucauld • Hôtel-Dieu

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

HÔTEL-DIEU
Centre d'Investigation en Médecine du Sport
CIMS

DOCUMENT A LIRE, A SIGNER et A DONNER A L'INFIRMIERE LE JOUR DE L'HOSPITALISATION

INFORMATION, CONSENTEMENT ET ENGAGEMENT DES PATIENTS AVANT INCLUSION DANS LE PROTOCOLE DE REHABILITATION PAR L'ACTIVITE PHYSIQUE

Madame, Monsieur,

Vous allez intégrer le protocole de réhabilitation par le sport de l'Hôtel-Dieu. Il s'agit d'une prise en charge médicale et hospitalière de votre pathologie. L'objectif est d'améliorer votre santé par la pratique d'une activité physique adaptée (APA) et régulière tout en recueillant des informations utiles à la recherche scientifique.

Votre prise en charge se déroulera sur une période d'un an. Elle débutera par une hospitalisation de jour permettant de faire un bilan objectif de vos capacités physiques et de votre état de santé : consultation de médecine du sport, questionnaires, test d'effort cardio-vasculaire, bilan sanguin, ostéodensitométrie, tests physiques.
Vous suivrez ensuite un protocole de 18 séances (3 séances par semaines pendant 6 semaines) de réhabilitation par le sport encadrées par des éducateurs en APA. Ces séances seront divisées en 2 parties : une première partie d'activité sur vélo ou tapis avec des exercices fractionnés, et une deuxième partie destinée à améliorer votre souplesse, au renforcement musculaire et au travail de posture et d'équilibre.
Au cours des 18 séances, vous serez vu chaque semaine par le médecin du sport afin de s'assurer qu'aucun problème n'entrave votre activité et afin de mesurer les premiers effets de la pratique d'une activité physique régulière. Un médecin spécialiste de votre pathologie principale vous verra également à mi-parcours.
A l'issu des 18 séances, nous vous proposerons la structure la plus adéquate pour poursuivre une activité physique ludique et adaptée à votre pathologie. Bien évidemment, nous insistons sur la nécessité d'être présent à chacune des 18 séances de réhabilitation sauf empêchement exceptionnel pour lequel vous aurez prévenu l'équipe au préalable.

Par ailleurs, nous allons évaluer les effets de l'activité physique sur votre santé en répétant les mêmes tests que ceux réalisés au cours de l'hospitalisation de jour initiale : à la fin du progamme, et à 6 mois et 1 an du début du protocole. De même, nous insistons pour que vous vous engagiez à venir réaliser ces bilans avec assiduité.

seront anonymisées lors de leur traitement statistique. Elles sont définies par la loi du 6 janvier 1978 (article 2), et soumises à la loi informatique, fichiers, libertés qui reconnaît 4 droits fondamentaux :

- droit d'information : toute personne a le droit de savoir si elle est fichée ;
- droit d'accès (de curiosité) : toute personne peut consulter ses données personnelles ;
- droit de rectification : toute personne peut rectifier, compléter, actualiser, verrouiller ou faire effacer des données erronées la concernant ;
- droit d'opposition : toute personne peut s'opposer sans justification à l'utilisation de données la concernant à des fins de prospection

Le protocole d'étude sera soumis au Comité de Protection des Personnes (CPP). Les informations nominatives et confidentielles seront supprimées au moment de la compilation informatique des résultats. Si vous le souhaitez, vous pourrez décider de vous retirer de l'étude à n'importe quel moment sans justification.

IDENTIFICATION DU SERVICE	IDENTIFICATION DU MEDECIN
Hôtel-Dieu PARIS Plateau de Réhabilitation par le sport 1, Place du Parvis Notre-Dame 75004 Paris Tél. : 01 42 34 78 47	

Ce document constitue une notice explicative du protocole qui vous est proposé.
Il ne constitue pas une décharge de responsabilité de l'équipe médicale qui vous prend en charge et qui vous a commenté ces informations générales en les rapportant à votre situation particulière.

J'accepte de participer au protocole de réhabilitation par le sport de l'Hôtel-Dieu et m'engage à être présent à chacune des étapes du protocole.

Fait à ....
En deux exemplaires dont un remis au patient
et l'autre conservé dans son dossier

Le ....

Signature du patient

1.4 Confidentiality Agreement

irmes

institut de recherche biomédicale et d'épidémiologie du sport

Institut de Recherche bioMédicale et Epidémiologie du Sport
http://www.insep.fr/fr/activites/recherchemedicales/Pages/IRMES-INSEP.aspx

Engagement relatif à la confidentialité et à la propriété intellectuelle

Dans l'exercice de mes fonctions de recherche à l'IRMES ou de mon stage à l'INSEP, j'aurai possiblement accès à des données confidentielles.

En signant ce formulaire, je reconnais que les travaux menés au sein de l'Institut et leurs résultats sont la propriété pleine et entière de l'IRMES et m'engage à :

1. assurer la confidentialité des données recueillies et, en particulier, à ne divulguer ni l'identité ni aucune donnée personnelle concernant les participants aux études menées ou initiées par l'Institut ;
2. assurer, de manière pérenne, la sécurité physique et informatique des données recueillies ;
3. ne pas conserver copie des documents présentant des données confidentielles ;
4. ne discuter des renseignements obtenus auprès des participants et recueillis dans les documents ou banques de données qu'avec les membres de l'Institut ayant signé le présent engagement ;
5. ne pas utiliser les données recueillies dans le cadre d'un projet à d'autres fins que celles prévues par son protocole ;
6. maintenir le secret professionnel à l'égard de tout tiers sur les activités de l'Institut ;
7. faire avaliser par le directeur de l'IRMES toute transmission, rapport, communication ou publications scientifiques qui pourraient résulter de ce travail.

Je soussigné, Stephanie Duncombe,

m'engage à respecter l'ensemble de ces clauses de confidentialité.

Signature

Date : 5 février 2019

Appendix 2 – Model Assumptions

The assumptions of the generalized linear models were tested. Normality of the dependent variable was assessed using a Shapiro-Wilk test, along with a histogram of the residuals to graphically view normality. A Q-Q plot was also created to examine the normality of the dependent variable and determined to follow a straight line. A scale-location plot was generated to test for homoscedasticity whilst a Breush-Pagan test was conducted to confirm no heteroscedasticity existed in the model. Residuals were plotted against fitted values to ensure residuals were randomly scattered around the 0-line suggesting equal variance of the error terms. Lastly a residuals vs leverage plot was created, and the plot was examined for points in the corners outside of Cook's distance. Points near this area were looked at for their influence on the model fit (Figure 7).

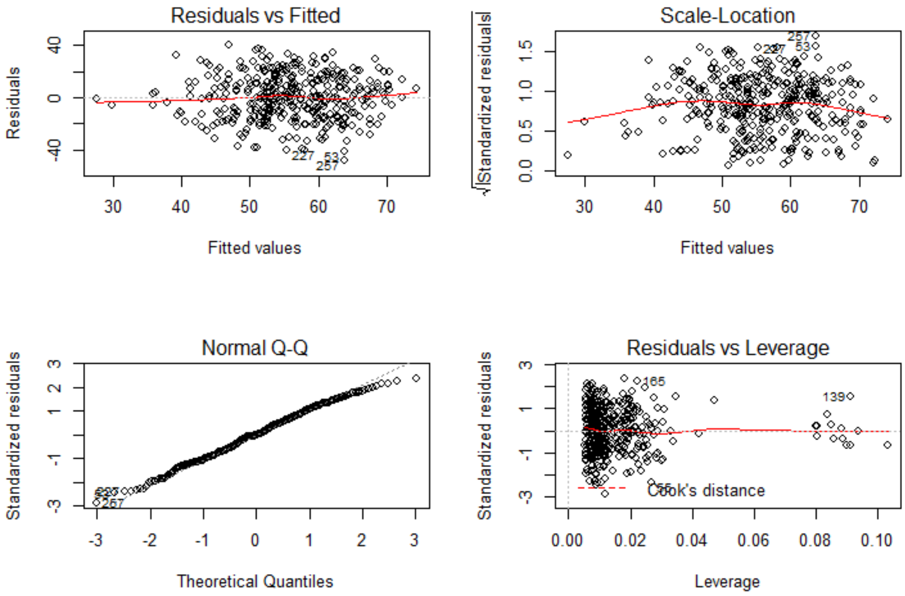

Figure 7. Residual Plots of SF-36 Physical requiring no modification to meet regression assumptions.

For the mixed-effects linear regression, residuals were once again plotted against the explanatory variables, and also against the fitted values. A histogram was drawn to confirm the normality of the residuals.

Appendix 3 – Example Regression Equation for Pre/Post Intervention Changes

Equation 4. Initial Regression Equation for the Change in PA levels including all variables with p <0.2

$$(RG\ Time\ 2 - RG\ Time\ 1) = \alpha_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_5 x_5 + \beta_6 x_6 + \beta_7 x_7 + \beta_8 x_8 + \beta_9 x_9 + \beta_{10} x_{10} + \beta_{11} x_{11} + \beta_{12} x_{12} + \beta_{13} x_{13} + \beta_{14} x_{14}$$

$\alpha_0 = intercept - representing\ mean\ change\ in\ R\&G\ score\ for\ a\ person\ with\ mean\ explanatory\ variables\ and\ no\ diagnosis$

$x_1 = mean\ centered\ R\&G\ score\ at\ baseline\ (continuous)$

$x_2 = mean\ centered\ BMI (continuous)$

$x_3 = mean\ centered\ age\ (continuous)$

$x_4 = mean\ centered\ comorbidity\ score\ (continuous)$

$x_5 = mean\ centered\ total\ medications\ (continuous)$

$x_6 = sex\ (binary: reference\ is\ female)$

$x_7 = mean\ centered\ number\ of\ intervention\ sessions\ attended\ (continuous)$

$x_8 = cancer\ (binary: reference\ is\ no\ cancer\ diagnosis)$

$x_9 = cardiometabolic\ (binary: reference\ is\ no\ cardiometabolic\ diagnosis)$

$x_{10} = respiratory\ (binary: reference\ is\ no\ respiratory\ diagnosis)$

$x_{11} = sleep\ apnea\ (binary: reference\ is\ no\ sleep\ apnea\ diagnosis)$

$x_{12} = HIV\ (binary: reference\ is\ no\ HIV\ diagnosis)$

$x_{13} = mental\ disorder\ except\ depression\ (binary: reference\ is\ no\ mental\ disorder\ diagnosis)$

$x_{14} = depression\ (binary: reference\ is\ no\ depression\ diagnosis)$

$x_{15} = neuromuscular\ (binary: reference\ is\ no\ neuromuscular\ diagnosis)$