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Cost-effectiveness of a proportionate universal offer of free exercise: Leeds Let's Get Active

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SUBJECT AREAS

Physical Medicine & Rehab Nutrition & Dietetics

KEYWORDS

physical activity, cost-effectiveness, free exercise, proportionate universal

Abstract

Objectives To assess the cost-effectiveness of a proportionate universal programme to reduce physical inactivity (Leeds Let's Get Active) in adults.

Methods A continuous-time Markov chain model was developed to assess the cost implications and QALY gains associated with increases in physical activity levels across the adult population. An ordered logistic model was specified to estimate the effectiveness of the Leeds Let's Get Active programme and derive transition probabilities between physical activity categories. A parametric survival analysis approach was applied to estimate the decay of intervention effect over time.

Baseline model data were obtained from previous economic models, population-based surveys and other published literature. A cost-utility analysis was conducted from a health care sector perspective over the programme duration (39 months). Scenario and probabilistic sensitivity analyses were performed to test the robustness of cost-effectiveness results.

Results 51,874 adult residents registered to the programme and provided baseline data, 19.5% of which were living in deprived areas. Under base case assumptions, Leeds Let's Get Active was found to be likely to be cost-effective. However, variations in key structural assumptions showed sensitivity of the results.

Conclusions Evidence from this study suggests that a universal offer of access to free off-peak leisure centre-based exercise that targets hard to reach groups can provide good value for money. Further data collection is needed to reduce the uncertainty surrounding the decision.

Introduction

Lack of regular physical activity (PA) is a major contributor to chronic disease and mortality in developed countries¹. Physical inactivity increases the risk of many chronic conditions, determining 9% of all premature mortality worldwide², and impacting substantially on national health care budgets³. In the UK, physical inactivity accounts for £1 billion a year to the national health system, with estimates rising to around £7.4 billion when taking a societal perspective⁴.

Cost-effectiveness analysis is used to inform decisions regarding which interventions should be

commissioned⁵. Evidence on the cost-effectiveness of PA interventions has accumulated over the last

two decades, though mostly on individual-level approaches⁶. While population-level interventions have been found to be cost-effective in the majority of cases, the number of these studies is currently limited, especially those assessing interventions aimed to reduce the number of physically inactive adults 7 .

Leeds Let's Get Active (LLGA) was a city-wide programme developed by the Local Authority and funded in collaboration with Sport England and Public Health England, which was aimed to reduce physical inactivity levels in the local adult population. The LLGA offer consisted of provision of universal access to free off-peak City Council leisure centre-based exercise sessions to all city residents. In order to encourage residents from low socio-economic backgrounds to take up the offer, LLGA sessions were provided in 17 centres located in the most deprived areas of the city. Exercise sessions included the use of free weight areas, swimming pool access and fitness classes. This form of LLGA ran for 39 months, from October 2013 to the end of December 2016. This paper reports the results of a cost-utility analysis to determine the cost-effectiveness of the LLGA programme.

Methods

Physical activity

At baseline and recruitment to the LLGA programme, participants were asked to self-report their current level of PA. This was based on a single-item question derived from the short-form IPAQ questionnaire⁸, which asked how many active days (defined as days with at least 30 minutes of at least moderate PA⁹) they had over the past week. Access to the free sessions was electronically monitored by means of a card participants were required to swipe at the leisure centre gates. No restrictions were imposed in terms frequency of access to the free exercise sessions. Following registration, a convenience sample of participants were surveyed a second time, either in person at the leisure centre or on-line.

Measures of behaviour change

In the cost-effectiveness analysis, programme effectiveness is defined as the ability of LLGA to affect a change in PA category. Four PA categories were defined according to the current UK PA

recommendations for adults¹⁰: inactive = zero, insufficiently active = 1 or 2, moderately active = 3 or 4, active = 5 to 7 active days a week. Two measures of behaviour change were available. The first (hereinafter "survey measure") was based on the survey data only, as the change in self-reported PA category observed between baseline and post-registration. The second measure (hereinafter "card swipe measure") was calculated as the probability of participants to improve baseline PA category due to a weekly access to LLGA sessions. Card swipe data were also analysed to obtain LLGA attendance drop-off patterns (i.e. time period between first and last LLGA session attended or end of the programme), which were used as a proxy for decay of intervention effect over time.

Analysis approach

For base-case estimation of effectiveness, a complete case analysis approach was applied in line with a previous similar study¹¹. An ordered logistic regression model was specified, with subsequent estimation of PA transition probabilities. Stata software version 14 was used for all regression analyses.

Intervention costs

Appendix I includes the financial audit reports provided by LLGA administrators which include the cost breakdown by project function/component. To align with the approach currently adopted to inform reimbursement decisions by the NHS¹², the budget expenditure was assumed to represent the opportunity cost of implementing the intervention, under a constrained budget at a current £20,000 - £30,000 willingness-to-pay (WTP) threshold range¹³. The unit programme cost was therefore calculated by dividing the allocated budget by the number of programme participants.

Decision-analytic model

Building on previous decision-analytic models¹¹ ¹⁴ ¹⁵, a continuous-time state-transition Markov model was developed to estimate incremental costs and QALYs associated with implementing a LLGA programme, relative to a no-intervention alternative, in the adult general population. A schematic of the model is shown in Fig. 1.

All participants start the model in the healthy state. This state is a nested Markov chain consisting of

four PA states. The model allows for transition between the four PA states over time. An integrated parametric survival approach allows for time-dependent PA transition probabilities to be specified. The model simulates progression from a healthy state, to death or any of the identified diseases from which a member can only stay or die in the subsequent cycles, until the cohort reaches 100 years of age.

Utility decrements were used to model utility losses due to a disease diagnosis. Seven chronic diseases and conditions were included ¹⁶. Specifically, Type II Diabetes, Coronary heart disease, Stroke, Colorectal, Breast cancer, Depression and Frailty syndrome. In line with the available evidence, the probability of developing a Frailty syndrome starts at age 65. Time-independent risks of developing one of the diseases are conditional on index of multiple deprivation (IMD) status (deprived or non-deprived) and PA level, which were assumed independent factors. In order to capture variations in utility due to changes in PA category before a diagnosis of disease, utility values were attached to each PA/IMD state. Once within a particular a disease state, a participant faced an increased probability of dying from all-causes. Thus, the 12 states represented constitute the four PA categories, the seven diseases and death.

Model parameters

Model parameters were sourced from previous economic models, published literature and national statistics, giving priority to UK-based evidence. Utility values, unit costs for treatment and management of the seven diseases, deprivation and PA gradients of morbidity and disease-related risks of all-cause mortality (i.e. relative risks) were searched using Medline database. Because there were insufficient published data describing all the differential risks, to estimate the relative risks for the intermediate categories, a linear interpolation method was employed as necessary, assuming a linear dose-response relationship. Table 1 reports the model baseline parameters and distributions.

Table 1
MODEL PARAMETERS AND DISTRIBUTIONS

Model parameters	Health state	Parameter	Source / Method	Distribution
Annual prob ACT	T2D	0.002 (0.002)	Joseph, et al. ²⁴	Beta
	CHD			Beta
	STR	0.011 (0.0031)	Sattelmair, et al. ²⁵	Beta
	CRC	0.003 (0.003)	Frew, et al. ¹¹	Beta

	BRC	0.011 (0.001)	Frew, et al. ¹¹	Beta	
DEP		0.011 (0.0106)	National Institute for	Beta	
			Health and Care		
			Excellence ²⁶		
	FRA	0.023 (0.023)	Fried, et al. ²⁷	Beta	
RR INA	T2D	1.700 (1.7)	Roux, et al. ¹⁵	LogNormal	
	CHD	1.500 (1.5)	Roux, et al. 15	LogNormal	
	STR	1.300 (1.3)	Roux, et al. 15	LogNormal	
	CRC	1.600 (1.6)	Roux, et al. 15	LogNormal	
	BRC	1.300 (1.3)	Roux, et al. 15	LogNormal	
	DEP	1.150 (1.15)	Meng and D'Arcy ²⁸	LogNormal	
	FRA	1.429 (1.43)	McPhee, et al. ²⁹	LogNormal	
RR INS	T2D	1.525 (1.52)	Linear interpolation	LogNormal	
	CHD	1.375 (1.137)	Linear interpolation	LogNormal	
	STR	1.225 (1.225)	Linear interpolation	LogNormal	
	CRC	1.450 (1.45)	Linear interpolation	LogNormal	
	BRC DEP	1.225 (1.225)	Linear interpolation	LogNormal	
	FRA	1.113 (1.11) 1.321 (1.32)	Linear interpolation Linear interpolation	LogNormal LogNormal	
RR MOD	T2D	1.292 (1.29)	Linear interpolation	LogNormal	
KK MOD	CHD	1.208 (1.208)	Linear interpolation	LogNormal	
	STR	1.125 (1.125)	Linear interpolation	LogNormal	
	CRC	1.250 (1.25)	Linear interpolation	LogNormal	
	BRC	1.125 (1.125)	Linear interpolation	LogNormal	
	DEP	1.063 (1.063)	Linear interpolation	LogNormal	
	FRA	1.179 (1.179)	Linear interpolation	LogNormal	
RR IMD	T2D	1.250 (0.041)	Sharma, et al. ³⁰	LogNormal	
	CHD	1.294 (1.29)	Bajekal, et al. ³¹	LogNormal	
	STR	1.400 (1.4)	Bray, et al. 32	LogNormal	
	CRC	1.100 (1.1)	Cancer Research UK		
			33		
	BRC	0.860 (0.86)	Cancer Research UK	LogNormal	
	DEP	1.170 (0.296)	Walters, et al. ³⁴	LogNormal	
	FRA	1.100 (0.11)	Curtis, et al. ³⁵	LogNormal	
RR death	T2D	1.850 (0.332)	Nwaneri, et al. ³⁶	LogNormal	
	CHD	1.900 (0.161)	Vlachopoulos, et al.	LogNormal	
		, ,	37		
	STR	1.900 (0.161)	Vlachopoulos, et al.	LogNormal	
	CRC	1.449 (1.45)	Cancer Australia ³⁸	LogNormal	
	BRC	1.320 (0.041)	Christiansen, et al.	LogNormal	
	DEP	1.520 (0.036)	Cuijpers, et al. ⁴⁰	LogNormal	
	FRA	2.700 (0.74)	Cuijpers, et al.	LogNormal	
Utility decrements	T2D	0.062 (0.06)	Kulmala, et al. ⁴¹ Sullivan and	Gamma	
othicy decrements			Ghushchyan ⁴²		
	CHD	0.056 (0.06)	Gulliford, et al. ¹⁴	Gamma	
	STR	0.101 (0.101)	Gulliford, et al. 14	Gamma	
	CRC	0.038 (0.038)	Gulliford, et al. ¹⁴	Gamma	
	BRC	0.015 (0.015)	Sullivan, et al. ⁴³	Gamma	
	DEP	0.130 (0.13)	Gulliford, et al. ¹⁴	Gamma	
	FRA	0.177 (0.18)	Lin of al 44	Gamma	
Utility values IMD	INA	0.935 (0.0221)	Lin, et al. ⁴⁴ HSE 2014 data	Beta	
NON-DEPRIVED			analysis		
	INS	0.985 (0.0218)	HSE 2014 data analysis	Beta	
	MOD	0.997 (0.0223)	HSE 2014 data analysis	Beta	
	ACT	0.982 (0.0219)	HSE 2014 data	Beta	
HELLE IMP	INIA	0.035 (0.0331)	analysis	Data	

Utility values ואט DEPRIVED	INA	0.935 (0.0221)	nse 2014 data analysis	вета
	INS	0.979 (0.0228)	HSE 2014 data analysis	Beta
	MOD	0.981 (0.0239)	HSE 2014 data analysis	Beta
	ACT	0.986 (0.0225)	HSE 2014 data analysis	Beta
Treatment and management costs	T2D	£ 1,363	Frew, et al. ¹¹	Fixed
	CHD1	£ 3,489	Frew, et al. ¹¹	Fixed
	CHD2	£ 105	Frew, et al. ¹¹	Fixed
	STR1	£ 9,630	Frew, et al. ¹¹	Fixed
	STR2	£ 2,396	Frew, et al. ¹¹	Fixed
	CRC	£ 9,999	Frew, et al. ¹¹	Fixed
	BRC	£ 9,091	Frew, et al. ¹¹	Fixed
	DEP	£ 139	Thomas and Morris	Fixed
	FRA	£ 3,351	McNamee, et al. ⁴⁶	Fixed

Notes: HSE = Health Survey for England; IMD = Index of Multiple Deprivation status; prob = probability; INA = inactive; INS = insufficiently active; MOD = moderately active; ACT = active; T2D = Type II Diabetes; CHD1 = Coronary Heart Disease, first year from event; CHD2 = Coronary Heart Disease, second and subsequent years; STR1 = Stroke, first year from event; STR2 = Stroke, second and subsequent years; CRC = Colorectal Cancer; BRC = Breast Cancer; DEP = Depression; FRA = Frailty syndrome, RR = Relative Risk

National life tables were used to inform time-dependent background mortality risks from all causes.

Utility data for the PA states were obtained from analysis of the Health Survey for England 2014 data.

Following the approach used in a relevant published study¹⁷, multivariate regressions were performed to estimate utility values as a function of IMD status and PA level.

The baseline PA category / number of active days was assumed to represent participants' PA habit before exposure to LLGA offer, which was assumed to remain constant over time (i.e. parallel trend assumption). The baseline age and proportions of PA habits in each of the two IMD deprivation groups corresponded to that of programme participants.

Economic evaluation

The decision problem was evaluated from a health care sector perspective, aligning the methods with previous economic evaluations¹¹ ¹⁴. A cost-utility analysis was conducted considering a programme duration time horizon to reflect a time that funders would find useful. Discount rate was set at an annual 1.5% for costs and outcomes. To facilitate the interpretation of cost-effectiveness results, the incremental net monetary benefit was calculated by multiplying the difference in QALYs between the two intervention options by £20,000 (lower bound of the WTP for a QALY gain), minus the costs associated with no-intervention¹⁸.

Sensitivity analysis

Scenario and probabilistic sensitivity analyses were performed to characterise the uncertainty surrounding the decision. First, an alternative lifetime time horizon was considered. Second, the measure of effectiveness was varied by using the card swipe data collected which implied that LLGA participants could only improve PA category by actively attending its free sessions. Third, a last-observation-carried-forward approach was applied to the survey measure. Therefore, zero change in PA level was assumed for participants for whom no follow-up outcome measurement was available. Finally, the assumption regarding the sustainability of the intervention over time was tested by assuming a no decay and a gradual return to baseline PA level (using the LLGA session drop-off pattern as a proxy).

A Monte Carlo simulation was used to propagate the uncertainty through the model and allow model parameters to vary simultaneously ¹⁸.

Results

51,874 adult residents registered to the LLGA programme and provided basic baseline data.

Participants were aged 39 years old on average, and the majority were female (62.4%) and living in non-deprived areas of the city (80.5%). A total of 191,605 LLGA sessions were accessed by 20,967

participants over the 39 months of programme.

Table 2 below reports the frequency distribution of PA categories observed at baseline and post-registration by IMD status. For 547 participants, full survey outcome data were available for the base-case analysis. Of these, 50.5% increased their baseline PA category, 36.9% did not change it, while 12.4% reported a lower PA level. Of the 20,967 participants attending at least one LLGA session, 529 improved their baseline PA category through a weekly participation to the free sessions. Participants from IMD deprived areas started at an overall lower PA level at baseline than the non-deprived group. Post-registration distributions of PA categories were found to be comparable between the two subgroups, indicating an only marginal difference in terms of intervention effect.

Table 2 Baseline and post-registration frequency distribution of PA categories

PA measurement	INA	INS	MOD	ACT	
(n)					
Baseline PA (n = 41,737) IMD non-deprived	28.1%	37.6%	21.7%	12.6%	
Baseline PA (n = 10,137) IMD deprived	32.8%	34.9%	20.1%	12.2%	
Post-registration survey (n = 461) IMD non-deprived	7.6%	32.7%	41.9%	17.8%	
Post-registration survey (n = 86) IMD deprived	5.8%	30.2%	46.5%	17.4%	
Post-registration card swipes IMD non-deprived (n = 17,460)*	24.3%	33.9%	23.8%	14.2%	
Post-registration card swipes IMD deprived (n = 3,507)*	27.7%	35.9%	22.9%	13.4%	
*a total of 529 improved baseline PA category within the first 6 months after registration.					
INA = inactive, INS = insufficiently active, MOD = moderately active, ACT = active. IMD = Index of Multiple					

Deprivation

Cost-effectiveness

Population-level costs, QALYs and incremental (deterministic) results are presented for the LLGA programme versus no scheme (see Table 3). Under base-case assumptions, LLGA shows to be the optimal strategy with an ICER of £555, well below the lower bound of the current WTP in the UK (£20,000) and providing an average positive INMB of £174 per participant. When varying the time horizon to a lifetime, LLGA becomes the dominant strategy, with negative incremental costs and QALY gains, and a per-participant INMB of £802. Comparable results are found when assuming no decay of intervention effectiveness over time and a gradual return to baseline PA level, with INMBs at £896 and at £619, respectively. Conversely, if effectiveness parameters are based on the card swipe measure or if zero change in PA category is assigned to participants not providing a follow-up survey measurement (last observation carried forward), LLGA is shown not to be cost-effective.

Table 3

Total costs, QALYs and incremental cost-effectiveness results: base-case vs scenario analysis

		Total cost (£)	Total QALY	Incremental cost (£)	Incremental QALY	cost per QALY (£)	Incremental Net Monetary Benefit
Base-case analysis (39 months)			3.0084 2.9994	£ 4.97	0.00896	£ 555	£ 174
Lifetime	LLGA	£ 158,385.94	25.9405	-£ 100.61	0.03506	Dominant	£ 802
	no LLGA	£ 158,486.55	25.9054				
Card swipe measure	LLGA no LLGA	£ 3,647.86	2.9995 2.9994	£ 29.18	0.00005	£ 567,088	-£ 28
Last observation carried forward	LLGA no LLGA		2.9995 2.9994	£ 29.24	0.00002	£ 1,315,249	-£ 29
No decay of intervention effect	no LLGA		3.0394 2.9994	-£ 96.06	0.03998	Dominant	£ 896
Gradual return to baseline PA level			3.0273 2.9994	-£ 61.29	0.02789	Dominant	£ 619

Figure 2 shows one thousand model iterations of the cost and QALY joint density plotted on a cost-effectiveness plane, comparing LLGA intervention to a no-intervention scenario (set as the origin), under base-case assumptions. Looking at the distribution of cost and QALY pairs, the majority fall below the WTP lower bound, indicating that there is a high probability of LLGA being the optimal alternative. Figure 3 shows the probability of LLGA being cost-effective, across a range of WTP thresholds. The cost-effectiveness acceptability curve (CEAC) did not cut the y-axis at zero (i.e. 55%) indicating that part of the joint density involved cost-savings¹⁹. Reflecting what was displayed in Fig. 2, there is a high probability (95%) of LLGA being the optimal strategy was found when considering a £20,000 threshold.

Discussion

Main findings

Results from this cost-utility analysis indicate that LLGA is likely to be cost-effective under base-case assumptions. The net benefits of implementing LLGA increase as a longer time horizon is considered. Scenario analyses also show that identification of the optimal strategy is highly dependent on variations to the effectiveness measure and key structural elements regarding the sustainability of

the intervention effect over time and assumed mechanisms of survey non-response.

Comparison with other studies

This study can be placed within the currently limited economic evaluation literature on populationlevel promotion of PA. In particular, the economic evaluation conducted to assess the costeffectiveness of the BeActive programme¹¹. This represents the main comparison study. LLGA mirrored the BeActive intervention modality, except that LLGA was offered only in City Council leisure centres located in the most deprived areas of the city. This afforded an opportunity to test the costeffectiveness of providing universal access to free off-peak leisure centre-based sessions in another similar setting. For BeActive, base-case cost-effectiveness estimates were not dissimilar from those reported here, with an estimated £400 incremental cost per QALY gained. This finding supports the hypothesis that this type of population-level intervention represents good value for money also in the short term, and even when the offer is proportionate to attract hard to reach groups. By contrast with this study, BeActive appeared to be cost-effective even under the most conservative assumptions, though no further details were reported. Another comparable study simulated the implementation of a primary care-based universal intervention and found a 64.7% probability of the intervention being cost-effectiveness at a WTP threshold of £30,000.14 One possible explanation for this difference in results is that, in that study, utility gains were accumulated only as a function of reduction in disease incidence and no utility gains were assigned from transitions to higher PA levels. Nevertheless, although some of the economic evaluation methods used in the present analysis were aligned with those studies (e.g. perspective, short time horizon), differences in the structures and parameters of the economic models limited the ability to directly compare our findings.

Strengths and limitations

To the best of our knowledge, this represents the first cost-utility analysis of a proportionate universal programme to promote free off-peak leisure centre-based exercise in the general population. The programme is relatively easy to incorporate into currently operating public leisure centres (off-peak sessions), and therefore this intervention has the potential to be replicated in other comparable

settings (i.e. local City Councils in the UK). As a result, this makes the evidence generated by this analysis particularly important for decision-makers that may be interested in evaluating the impact of implementing this type of intervention in the future.

The study is however subject to a number of limitations. In particular were the lack of experimental design, a non-research led data collection and handling process and restrictions imposed in terms of further data collection on residents/participants. This meant making the validity of effectiveness results depend on the plausibility of a parallel trend assumption, representativeness of the sample of participants providing full outcome data, as well as on untested measures of PA behaviour change which in turn relied on self-report. Previous similar studies share these limitations that cannot be overcome retrospectively and are likely to characterise large-scale programmes. Furthermore, while a sub-group analysis was conducted to account for heterogeneous effects, one of the objective of public health decision-makers is to reduce existing health inequality, which, due to resource constraints, was not possible to ascertain within this study.

Application of the QALY as the consequence considered in the evaluation restricted the evaluative space accordingly, therefore excluding non-health effects potentially generated by the intervention (e.g. increased work-related productivity²⁰). However, in line with previous models^{11 15 21}, the decision-analytic model used for economic evaluation of LLGA was designed to accumulate utility gains/losses as a result of changes in PA state.

A de novo decision-analytic model was developed building on previous models, by incorporating a continuous-time structure which allowed for testing the assumption related to the sustainability of behaviour change over time. Nonetheless, this analysis still relied upon other structural assumptions relating to a fully elastic dose-response relationship between changes in PA and health, compensatory or synergistic effects potentially occurred on the path to health improvement (e.g. changes in dietary habits), increased health expenditure from extended life expectancy, and adverse events (e.g. injuries) which were not formally taken into account. Nevertheless, unlike previous models, negative intervention effects were captured informally by allowing the four PA states to move freely between one another.

Further, these results, like those presented in previous similar studies, rely on a set of structural assumptions which have not been verified yet and have the potential to impact identification of the optimal intervention. In particular, although the decision-analytic model used for this economic evaluation allows for "natural" transitions between PA states to be captured, due to lack of relevant data, PA states were assumed to be stable over time in absence of the intervention. However, this may not always be necessarily the case, especially in the short term ²² and during sensitive life phases (e.g. retirement ²³). Furthermore, since the effects of changes in PA on chronic disease are likely to vary between conditions and depend on personal characteristics, as well as on their magnitude/persistence, population-level monitoring studies should deal with these aspects. In addition, the impact of an intervention like LLGA is likely to vary not only between individuals and over time, but also on whose economic perspective is taken. In this and previous studies 11 14, costs and benefits (QALYs) falling on the health care sector only were considered. However, results are likely to change when a local public health agency viewpoint is taken. As the body administering and hosting the intervention, the opportunity cost by the Local Authority may not coincide with the budget expenditure. Potential spill-overs from increased numbers of paying members or reductions in member retention due to the intervention might have occurred.

Implications for future research

The results presented here contribute new economic information regarding the value for money of universal programmes to reduce physical inactivity in the general population. A number of limitations have been noted with the analysis reported here, many of which relate to the paucity of data to inform such analysis and a lack of consensus on methodological approaches. Future work should focus on better data collection and assessing the value for money of this type of population-level programmes to inform decisions that often are made outside the health care sector.

Declarations

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

No data are available. Programme data have been provided by the local City Council under a Data Processing Agreement.

Competing interests

There are no competing interests for any author.

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Authors contributions

PC was responsible for designing the study, data analysis, development of the economic model and drafting the manuscript. DM, AJH and LB contributed to the writing of the manuscript. All authors read and approved the final version of the manuscript.

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Figures

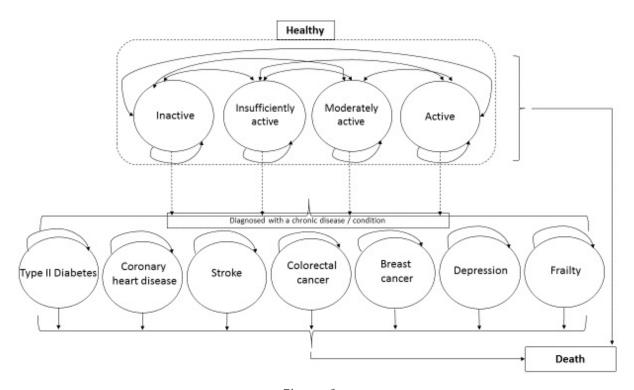


Figure 1
Schematic of the Markov model

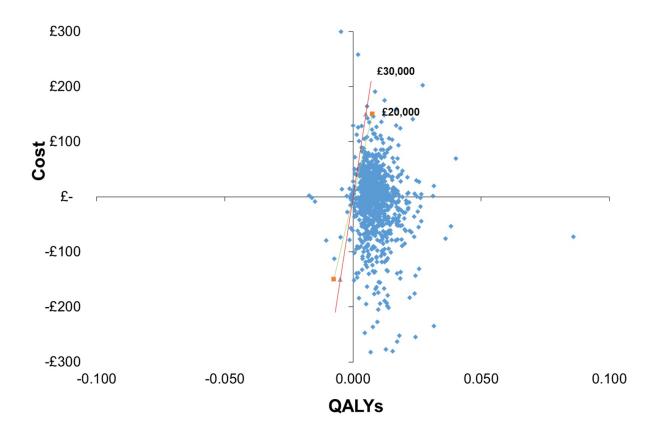


Figure 2
Cost-effectiveness plane

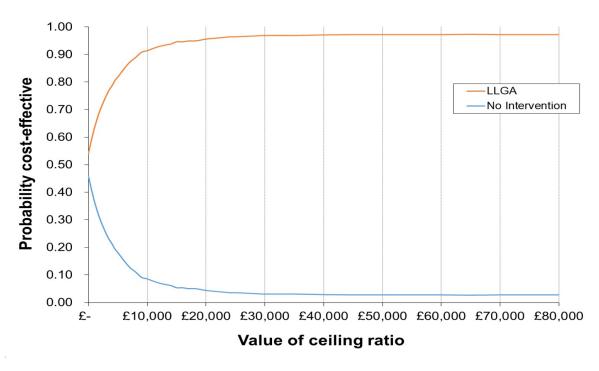


Figure 3

Cost-effectiveness acceptability curve

Supplementary Files

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