OBJECTIVELY MEASURED SEDENTARY TIME AND ASSOCIATIONS WITH INSULIN SENSITIVITY: IMPORTANCE OF REALLOCATING SEDENTARY TIME TO PHYSICAL ACTIVITY

Running head: Reallocating sedentary time to physical activity

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Objective: To quantify associations between objectively measured sedentary time and markers of insulin sensitivity by considering allocation into light-intensity physical activity or moderate- to vigorous-intensity physical activity (MVPA).

Methods: Participants with an increased risk of impaired glucose regulation (IGR) were recruited (Leicestershire, United Kingdom, 2010-2011). Sedentary, light-intensity physical activity and MVPA time were measured using accelerometers. Fasting and 2-hour post-challenge insulin and glucose were assessed; insulin sensitivity was calculated by HOMA-IS and Matsuda-ISI. Isotemporal substitution regression models were used. Data were analysed in 2014.

Results: 508 participants were included (average age = 65 years, female = 34%). Reallocating 30 minutes of sedentary time into light-intensity physical activity was associated a 5% (95% CI 1, 9%; p = 0.024) difference in Matsuda-ISI after adjustment for measured confounding variables. Reallocation into MVPA was associated with a 15% (7, 25%; p < 0.001) difference in HOMA-IS and 18% (8, 28%; p <0.001) difference in Matsuda-ISI. Results for light-intensity physical activity were modified by IGR status with stronger associations seen in those with IGR.

Conclusions: Reallocating sedentary time into light-intensity physical activity or MVPA was associated with differences in insulin sensitivity, with stronger and more consistent associations seen for MVPA.

Key words: *glucose; insulin sensitivity; isotemporal substitution; physical activity; sedentary behaviour*

BACKGROUND

Over recent years, there has been mounting evidence suggesting that sedentary behaviour, defined as any sitting or lying time less than 1.5 METS during waking hours [1], is an independent determinant of chronic disease and all-cause mortality [2,3]. The most consistent and strongest associations have been with metabolic health and type 2 diabetes [4]. However, there has been ongoing debate about whether the deleterious associations of sedentary behaviour are independent to the beneficial associations of greater physical activity. Studies that have employed accelerometer-based quantification of movement have drawn differing conclusions, even when reporting data from the same cohort [5,6].

During waking hours it is not possible to alter sedentary time whilst keeping time in other forms of physical activity constant; for example, reducing sedentary time by 30 minutes necessitates a 30 minute increase in some form of light-to-vigorous intensity physical activity. This fact is often overlooked in epidemiological research and may explain reported discrepancies in the literature.

Isotemporal substitution has been promoted as an appropriate model for investigating associations of health behaviours with finite boundaries, such as energy intake or time in physical activity during waking hours [7]. Isotemporal substitution can be used to model associations with health of reallocating one behaviour for another, which is particularly useful to sedentary behaviour research. In modern environments, humans spend the majority of their waking hours sedentary [2], therefore investigating the associations of reallocating this dominant behaviour into others is important. For example, analysis of accelerometer data from NHANES reported that reallocating 30 minutes of sedentary time

to light-intensity physical activity was associated with 1.9% lower blood triglyceride levels and 2.4% lower insulin levels with stronger associations shown for reallocation into MVPA [8]. Buman and colleagues also reported that reallocating objectively assessed sedentary time for light activity was associated with better physical health and well-being in older adults [9]. We extend these observations in the general population to investigate the associations of reallocating sedentary time to light-intensity physical activity or moderate- to vigorous-intensity physical activity (MVPA) with markers of glucose regulation and insulin sensitivity in a primary care population at increased risk of type 2 diabetes.

METHODS

PARTICIPANTS

This study reports baseline data from the Walking Away from Type 2 Diabetes study, the methods of which have been published elsewhere [10]. A total of 833 participants at increased risk of type 2 diabetes were recruited through 10 primary care practices in Leicestershire, UK, in 2010-2011; the analysis was conducted in 2014. Individuals with an increased risk of impaired glucose regulation (IGR) (composite of impaired glucose tolerance (IGT) and/or impaired fasting glycaemia (IFG) and/or undiagnosed type 2 diabetes) were identified using a modified version of the Leicester Risk Score[11]. Those individuals scoring within the 90th percentile in each practice were invited to take part in the study. This approach has reasonable sensitivity and specificity for identifying participants with IGR [11,12]. Individuals were unaware of their diabetes risk status before entering the study. We excluded those who had previously diagnosed type 2 diabetes, were currently taking steroids or were unable to take part in any walking activity.

ETHICS

Ethical approval was obtained from the Nottingham Research Ethics Committee, UK. Written informed consent was provided by all participants.

OBJECTIVE SEDENTARY AND PHSYICAL ACTIVITY TIME ASSESSMENT

Participants were asked to wear a tri-axial accelerometer (Actigraph GT3X, Pensacola, FL, USA), for a minimum of seven consecutive days during waking hours. Data were recorded in 15 second epochs. Previously used cut-points were employed to categorise time spent in sedentary behaviours (<25 counts per 15 seconds), time in light-intensity physical activity (≥25 to <488 counts per 15 seconds) and time in MVPA (≥488 counts per 15 seconds) from the vertical axis [13].

Non-wear time was defined as a minimum of 60 minutes of continuous zero counts. At least 600 minutes of wear time per day were considered valid. For inclusion in these analyses, participants were required at have at least four days of valid accelerometer data [14]. A commercially available data analysis tool (KineSoft version 3.3.76, Kinesoft, New Brunswick, Canada; www.kinesoft.org) was used to process accelerometer data.

DEMOGRAPHIC, ANTHROPOMETRIC, LIFESTYLE AND BIOCHEMICAL MEASUREMENTS

Medication, ethnicity and smoking status were obtained following an interview-administered questionnaire conducted by a healthcare professional. Social deprivation was determined by assigning an Index of Multiple Deprivation (IMD) score to the participant's residential area. IMD scores are publically available continuous measures of compound

social and material deprivation. Body weight (Tanita TBE 611, Tanita, West Drayton, UK), waist circumference (midpoint between the lower costal margin and iliac crest) and height were measured to the nearest 0.1 kg and 0.5 cm respectively.

All participants underwent a standardised oral glucose tolerance test. Participants were asked to fast from 10pm on the evening before the test and to avoid vigorous-intensity physical activity in the preceding 24 hours. Fasting and 2-hour post 75g glucose challenge (2-h) samples were measured within the same laboratory at the Leicester Royal Infirmary, Leicestershire, UK, using a glucose oxidase method on the Beckman Auto Analyzer (Beckman, High Wycombe, UK). Plasma samples for fasting and 2-h insulin analysis were frozen within a -80oC freezer and analysed at the end of baseline data collection using an enzyme immuno-assay (80-INSHU-E01.1, E10.1 Alpco Diagnostics 26G Keewaydin Drive, Salem, NH 03079 USA). Insulin analysis was undertaken within a specialist laboratory by Unilever R&D, Bedfordshire, UK. Due to the cessation of bleeding or insufficient plasma volumes, both fasting and 2-h insulin samples were available for 583 (70%) participants.

Measures of insulin sensitivity

HOMA-IS and Matsuda-ISI were used to calculate insulin sensitivity:

HOMA-IS [15] = 1/HOMA-IR = $22.5/(G_0 \cdot I_0)$

Matsuda-ISI [16]= $10000/\mathrm{sqrt}(G_0 \cdot I_0 \cdot G_{120} \cdot I_{120})$

These models are commonly used indexes of insulin sensitivity in epidemiological research and have been shown to correlate reasonably with gold standard measures of insulin sensitivity and/or progression to type 2 diabetes [17,18]. Matsuda-ISI is more likely to

reflect factors related to insulin release and peripheral insulin resistance whereas HOMA-IS may be a better measure of hepatic insulin resistance [19].

STATISTICAL ANALYSIS

Linear regression modelling employing an isotemporal substitution approach was used to quantify the association of substituting sedentary behaviour for light-intensity physical activity or MVPA on markers of glucose regulation and insulin sensitivity. Isotemporal substitution specifically takes into account that, in behavioural terms, time is not infinite; spending more time in one kind of activity requires less time spent in other activities during waking hours. Consequently it has been recommended for use in observational research employing time based measures of physical activity [7,8,20].

In order to investigate the association between sedentary behaviour and insulin sensitivity, isotemporal substitution requires that average wear time, time in light-intensity physical activity and time in MVPA are simultaneously entered into a linear regression model; the resulting regression coefficient for light-intensity physical activity and MVPA represent the association of substituting a given unit of sedentary time into each category, respectively [7]. Each model was further adjusted for measured potential confounding variables defined as age, sex, ethnicity, social deprivation, smoking status, and beta-blocker and statin medication status. In addition, results were further adjusted for BMI. Interaction terms were fitted to assess whether the association of light-intensity physical activity or MVPA with measures of insulin sensitivity were modified by sex or IGR status; for the purposes of this analysis IGR was defined as: fasting glucose ≥ 6.0 mmol/l and/or 2-hour glucose ≥ 7.8 mmol/l and/or HbA1c ≥ 6.0%. The derived indexes of insulin sensitivity displayed non-

parametric distributions, therefore all dependant variables were log-transformed with resulting regression coefficients back transformed; displayed coefficients consequently represent the value by which the dependant variable is multiplied by for a given unit of time in light-intensity physical activity or MVPA. We display results per 30 minutes difference for ease of interpretation.

We undertook a sensitivity analysis to establish whether associations of light-intensity physical activity with measures of insulin sensitivity were affected if a lower definition of MVPA was used. Whilst the primary definition of MVPA used in this analysis has been extensively employed in epidemiological research across a wide range of populations [8,21-23], lower cut-points for older adults have been suggested [24]. Given the older nature of our cohort, for the sensitivity analysis we used an MVPA cut-point specifically developed in older adults (≥260 counts per 15 seconds) [24]. Others have also used this threshold in epidemiological research [9]. This lower threshold is likely to include a higher proportion of incidental activity (i.e. light house work) compared to higher thresholds.

We further sought to determine whether differences in the strength of association of time in light-intensity physical activity and MVPA with measures of insulin sensitivity were mediated by the total volume of physical activity undertaken. Total accelerometer counts (a measure of physical activity volume derived by the intensity and frequency of accelerations undertaken) were highly correlated with time in MVPA, thus prohibiting adjustment for each other in the same model. As an alternative, we undertook a further isotemporal model to investigate whether reallocating a unit of physical activity volume (100,000 counts per day) from the light-intensity physical activity category into MVPA was further associated with indices of insulin sensitivity.

Assumptions of linearity for each model were verified and multicollinearity was checked using the variance inflation factor (VIF). VIF values in all models were less than 5 indicating that multicollinearity was low. $P < 0.05$ was considered significant for main effects and $P < 0.1$ for interactions. All statistical analyses were conducted using IBM SPSS Statistics v20.0.

RESULTS

Seven hundred and twenty seven participants (87%) had valid accelerometer data. Of these 508 had both fasting and 2-h insulin levels and were included in this study. Those with missing data were younger (62.1 years for missing vs. 63.8 years complete; $p = 0.004$), were more likely to be female (41% vs. 34%; $p = 0.042$) and more likely to be from a Black and minority ethnic population (15 vs. 10%; $p = 0.012$) than those with complete data. However, there was no difference in BMI, fasting glucose or 2-h glucose.

Table 1 displays the characteristics of the included participants, and Table 2 displays the results of the isotemporal substitution model. Reallocating 30 minutes per day of sedentary time into light-intensity physical activity was associated with a 5% (1 - 9%; $p = 0.024$) difference in Matsuda-ISI. No associations were seen for HOMA-IS, however significant associations were observed for 2-h glucose and 2-h insulin (Table 2). Reallocating 30 minutes per day of sedentary time into MVPA was associated with a 15% (7 – 25%; $p < 0.001$) difference in HOMA-IS and 18% (8 – 28%; $p <0.001$) difference in Matsuda-ISI. Inverse associations were also seen for fasting and 2-h insulin (Table 2).

Results for MVPA and light-intensity physical activity were largely unaffected by further adjustment for BMI (Table 2). There was no interaction by sex for any measure ($p>0.1$).

However, results were modified by IGR status (Table 3). The association of reallocating sedentary time into light-intensity physical activity was stronger in those with IGR, whereas associations with MVPA were largely unaffected by IGR status (Table 3).

Results for associations of light-intensity physical activity with insulin sensitivity were attenuated in the full cohort when the lower definition of MVPA was used; however results remained significant in those with IGR (Supplementary Table 1)

Reallocating a fixed measure volume of physical activity from light-intensity to MVPA was not associated with additional differences in measures of insulin sensitivity (Supplementary Table 2).

DISCUSSION

Reallocation of sedentary time into either light-intensity physical activity or MVPA was associated with enhanced insulin sensitivity in those with an increased risk of type 2 diabetes, with more consistent and stronger associations seen for MVPA. For example, reallocating sedentary time into light-intensity physical activity and MVPA were associated with differences in Matsuda-ISI; however over 1.5 hours of reallocation into light-intensity physical activity was needed to gain an equivalent difference as that observed for 30 minutes of MVPA. The stronger associations with MVPA appeared to be primarily driven by the greater physical activity volume accumulated per unit time rather than intensity *per se*. Results for light-intensity physical activity were significantly modified by IGR status with stronger associations seen in those with IGR. To our knowledge this is the first study to quantify associations of sedentary behaviour on common indexes of insulin sensitivity in a population with an increased risk of type 2 diabetes.

Our results are similar to the only other study using an isotemporal substitution approach to quantify the association of objectively measured sedentary behaviour with markers of insulin sensitivity. Using data from a sub-sample of NHANES, Buman et al found that substituting sedentary time into light-intensity physical activity was associated with fasting insulin, but with stronger associations for MVPA [8]. Other studies that have adjusted for MVPA have also found a link between metabolic health and sedentary behaviour [21,22], although associations in some studies have been weak or non-significant [6]. Importantly we show that results for reallocating sedentary time into light-intensity physical activity were significantly modified by IGR status, with meaningful associations only observed in those with IGR. The potential importance of substituting sedentary behaviour for light-intensity physical activity in those with IGR is broadly consistent with intervention studies in those with a high risk of, or diagnosed, type 2 diabetes, where improvements in measures of glycaemia or insulin sensitivity have been shown following light-intensity exercise training [25-29]. Of particular relevance, when light-intensity and moderate-intensity exercise training programmes were matched for total volume in those with type 2 diabetes, similar reductions in HbA1c were reported [26]. This is consistent with a recent meta-analysis of exercise training studies in those with type 2 diabetes that concluded that exercise volume, but not intensity, was a significant determinant of change in HbA1c [30,31]. Therefore, our study adds to this evidence by emphasising the potential clinical relevance of increasing physical activity volume throughout the day, regardless of intensity, in those with IGR. However, we show that these results may not be generalizable to those with normal glucose control as only time in MVPA was associated with differences in insulin sensitivity in this group; this finding requires further investigation.

Whilst evidence for light-intensity physical activity in the promotion of metabolic health in high risk populations continues to mount, few studies have assessed the impact of directly reducing sedentary behaviour. Dunstan and colleagues recently reported that postprandial glucose was significantly reduced in overweight and obese participants when sedentary behaviour was broken by regular bouts of light-intensity walking [32], although additional benefits were not seen with moderate-intensity walking. More recently, a six month behavioural intervention aimed at reducing sedentary behaviour led to improvements in fasting insulin and HOMA-IS [33,34]. In contrast, another study reported metabolic improvements following a sedentary behaviour intervention were only observed when combined with exercise training [34]. The strengths of our study include robust measures of fasting and 2-h measures of glucose and insulin, recruitment of those with an increased risk of type 2 diabetes from primary care making the results broadly generalizable to those referred into diabetes prevention programmes, objectively measured sedentary behaviour and physical activity, and an analysis plan which encompassed the full measurement period through isotemporal substitution.

The primary limitation is the cross-sectional design which negates the ability to infer causation and allows for the possibility that unmeasured variables, such as dietary quality, may be confounding the results. The cross-sectional design also means that the isotemporal substitution approach used in this study is not based on actual behavioural reallocation by individuals within the cohort, but instead should be viewed as population level modelling study. In addition, we did not measure sleep duration and were thus only able to investigate the importance of behavioural allocation during waking hours; this is similar to the approach that others have used with self-reported measures of physical activity [7,20]. Moreover,

only a small minority of individuals engage in excessive sleeping behaviour (>8 to 9 hours) [35,36], therefore advocating increased physical activity at the expense of sleep is unlikely to be an applicable behavioural approach. However, reallocating sedentary time to sleep has been associated with improved metabolic health and represents an alternative strategy to the one presented here [8]. The objective measure of sedentary behaviour employed in this study does not directly assess postural allocation, but relies on categorising behaviours on the frequency and intensity of movement undertaken. The degree of missing data also potentially limits generalizability. Finally given the high risk nature of the cohort, the results are not necessarily generalizable to the general population.

Conclusion

Our study highlights the importance of considering the full spectrum of physical activity conducted in waking hours and supports the potential benefits of focusing on sedentary behaviour as a specific target for intervention. Whilst substituting sedentary behaviour for any form of movement may be clinically important, especially in at-risk populations with IGR, the intensity of the substituted behaviour is likely to be key in determining the extent of the resulting health benefits, primarily through maximising the overall volume of physical activity accumulated in a given period of time. Given some sedentary time is unavoidable in modern working and living environments, a simple behavioural rule of thumb for those with an increased risk of diabetes could simply be: when sedentary, undertake light-intensity movement where possible (such as light-ambulation); when undertaking light-intensity movement increase to a moderate-intensity where possible (i.e. purposeful walking). However, given the study design and limitations, this study does not confirm causality and thus intervention studies are needed to establish the efficacy of such behavioural approaches.

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Table 1: Characteristics of the 508 participants, Leicestershire, UK, 2010-2011

Characteristics	**Median (IQR)/Number (%)**
Age (years)	65 (60 – 69)
Sex (female)	174 (34)
Ethnicity	
White European	458 (90)
South Asian	35 (7)
Other	15 (3)
Deprivation score	12.6 (7.5 – 21.6)
Current smoker	45 (9)
Impaired glucose regulation	259 (51)
Statin medication	165 (32)
Beta-blocker medication	81 (16)
BMI (kg/m^2)	31.6 (28.5 – 35.0)
Fasting glucose (mmol/l)	5.2 (4.9 – 5.7)
2-hour glucose (mmol/l)	6.0 (4.8 – 7.8)
Fasting insulin (mU/l)	8.9 (6.1 – 12.9)
2-insulin (mU/l)	46.7 (25.8 – 82.3)
Accelerometer data	
Total volume (1000 counts per day)	232.6 (171.4 – 318.9)
Time Sedentary (mins/day)	607.0 (549.9 – 607.8)
Time in light-intensity physical activity (mins/day)	205.3 (170.5 – 250.6)
Time in moderate- to vigorous-intensity physical activity (mins/day)	29.8 (17.6 – 50.5)
Wear time (mins per day)	859.4 (803.2 – 907.3)

Table 2: Association of substituting 30 minutes of sedentary behaviour for light-intensity physical or MVPA with measures of insulin sensitivity and glucose regulation using isotemporal substitution,Leicestershire, UK, 2010-2011

	Model 1				Model 2			
Outcome	**Sedentary to Light**	***P* value**	**Sedentary to MVPA**	***P* value**	**Sedentary to Light**	***P* value**	**Sedentary to MVPA**	***P* value**
Fasting glucose	1.00 (0.99, 1.01)	0.389	1.00 (0.98, 1.01)	0.804	1.00 (0.99, 1.01)	0.348	1.00 (0.98, 1.02)	0.998
Fasting insulin	0.98 (0.95, 1.01)	0.255	0.87 (0.81, 0.93)	<0.001	0.99 (0.96, 1.02)	0.547	0.92 (0.86, 0.99)	0.022
2-h glucose	0.97 (0.95, 0.99)	< 0.001	0.98 (0.95, 1.02)	0.431	0.97 (0.95, 0.99)	< 0.001	0.98 (0.94, 1.02)	0.369
2-h insulin	0.96 (0.92, 1.00)	0.044	0.84 (0.76, 0.92)	0.001	0.96 (0.91, 1.00)	0.055	0.85 (0.77, 0.94)	0.002
HOMA-IS	1.02 (0.98, 1.05)	0.375	1.15 (1.07, 1.25)	<0.001	1.01 (0.97, 1.04)	0.719	1.08 (1.01, 1.16)	0.034
Matsuda-ISI	1.05 (1.01, 1.09)	0.024	1.18 (1.08, 1.29)	<0.001	1.04 (1.00, 1.08)	0.044	1.14 (1.04, 1.25)	0.007

Abbreviations: MVPA, Moderate-to-vigorous physical activity.

Coefficients represent the factor by which the measure of insulin sensitivity is multiplied by (95% Confidence Interval) for a 30 minute difference in the substituted physical activity behaviour

Model 1: Adjusted for ethnicity, sex, smoking status, age, beta-blocker and statin medication status, IMD score

Model 2: Adjusted for all of the confounders included in Model 1 plus Body Mass Index

Table 3: Associations of substituting 30 minutes of sedentary behaviour for light-intensity physical or MVPA with measures of insulin sensitivity, stratified by IGR status,Leicestershire, UK, 2010-2011

	Normal glucose metabolism				IGR					
Outcome	**Sedentary to Light**	***P* value**	**Sedentary to MVPA**	***P* value**	**Sedentary to Light**	***P* value**	**Sedentary to MVPA**	***P* value**	***P* for light x IGR interaction**	***P* for MVPA x IGR interaction**
HOMA-IS	0.97 (0.92, 1.01)	0.145	1.15 (1.04, 1.27)	0.006	1.07 (1.02, 1.12)	0.006	1.11 (0.99, 1.24)	0.063	0.001	0.370
Matsuda-ISI	1.00 (0.95, 1.06)	0.910	1.17 (1.05, 1.32)	<0.001	1.09 (1.03, 1.15)	0.003	1.11 (0.97, 1.25)	0.119	0.029	0.879

Abbreviations: IGR, Impaired Glucose Regulation; MVPA, Moderate-to-vigorous physical activity.

Coefficients represent the factor by which the measure of insulin sensitivity is multiplied by (95% Confidence Interval) for a 30 minute difference in the substituted physical activity behaviour.

Coefficients were adjusted for ethnicity, sex, smoking status, age, beta-blocker and statin medication status, and IMD score.

Supplementary Table 1: Associations of substituting 30 minutes of sedentary behaviour for light-intensity physical or MVPA (defined as ≥260 counts per 15 seconds) with measures of insulin sensitivity using isotemporal substitution in the full Walking Away cohort and stratified by impaired glucose regulation (IGR) status, Leicestershire, UK, 2010-2011

Full Cohort

Outcome	Sedentary to Light	*P* value	Sedentary to MVPA	*P* value
HOMA-IS	1.01 (0.96, 1.06)	0.679	1.08 (1.03, 1.13)	0.001
Matsuda-ISI	1.04 (0.98, 1.11)	0.175	1.12 (1.05, 1.18)	<0.001

Stratified by IGR status

	Normal glucose metabolism				IGR					
Outcome	**Sedentary to Light**	***P* value**	**Sedentary to MVPA**	***P* value**	**Sedentary to Light**	***P* value**	**Sedentary to MVPA**	***P* value**	***P* for light x IGR interaction**	***P* for MVPA x IGR interaction**
HOMA-IS	0.94 (0.88, 1.00)	0.051	1.09 (1.02, 1.16)	0.015	1.08 (1.01, 1.16)	0.016	1.06 (1.00, 1.13)	0.069	<0.001	0.238
Matsuda-ISI	0.98 (0.90, 1.06)	0.623	1.11 (1.02, 1.20)	0.012	1.09 (1.01, 1.18)	0.022	1.09 (1.01, 1.18)	0.036	0.018	0.474

Coefficients represent the factor by which the measure of insulin sensitivity is multiplied by (95% Confidence Interval) for a 30 minute difference in the reallocated physical activity behaviour. Coefficients were adjusted for ethnicity, sex, smoking status, age, beta-blocker and statin medication status, and IMD score.

Supplementary Table 2: Association of substituting the same physical activity volume (accelerometer counts) from light-intensity physical activity to MVPA with measures of insulin sensitivity

Outcome	Light-intensity physical activity to MVPA	*P* value
HOMA-IS	1.06 (0.89, 1.27)	0.491
Matsuda-ISI	0.94 (0.76, 1.16)	0.580

Coefficients (95% Confidence Interval) represent the factor by which the measures of insulin sensitivity are multiplied by when substituting 100,000 counts/day from light-intensity physical activity to MVPA. Coefficients were adjusted for wear time, ethnicity, sex, smoking status, age, beta-blocker and statin medication status, and IMD score.