Early detection methods to assess the risk of pressure ulcers in individuals with mental illness

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Introduction

Pressure ulcers (PUs), also called pressure sores or bedsores, can develop if an individual spends too long **sitting or lying in one position**. Those at particular risk include people with **mental health conditions** (dementia, schizophrenia, severe depression etc.). Indeed, a recent study reported that individuals with dementia are predisposed to a higher prevalence of PUs compared to those with other comorbidities (diabetes, ischaemic heart disease, lung disease and chronic renal failure) [Jaul, 2017a]. The increased risk is due to several factors including:

- Inability to change position without assistance
- Poor diet and dehydration, poor blood supply, agitation or restlessness
- Medication and communication issues.

Effective strategies for PU prevention would lead to a higher survival rate and improved individual quality of life in the dementia population [Jaul, 2017a; Lee, 2018]. It has also been suggested that increased clinician awareness of PU risk in early to moderate dementia may suppress their accelerated development, resulting in less patient suffering and reduced long-term care hospitalization [Jaul, 2017b].

There is a growing interest in examining the skin response to mechanical-induced damage by collecting and analysing biomarker release following loading. As an example, the up-regulation of pro-inflammatory cytokines is becoming a well-established indicator of skin damage following a mechanical insult e.g. tape stripping of the stratum corneum [De Jongh, 2007]. These biomarkers can be collected in sebum using a non-invasive micro-porous film mounted on skin surface. This approach has been adopted to examine the response of the loaded skin following the application of medical devices, such as respiratory face masks [Worsley, 2016] and

spine boards [Hemmes, 2017], as well as examining the differential response of skin to compression and shear forces [de Wert, 2015; Soetens, 2019]. In each case, the mechanical loading produced an up-regulation of cytokines, notably IL-1α, although these studies were generally confined to a small cohort of young able-bodied participants. In addition, in a small clinical study of patients with a Category I pressure ulcer over the sacrum, there was a localised and persistent up-regulation of the cytokine [Cornelissen, 2010]. The studies, to date, therefore reflect a controlled environment for the sampling of biomarkers and further research is required to establish the clinical translation of this technique. This provides the motivation for the current work to examine the feasibility of monitoring skin surface biomarkers in both an elderly able-bodied cohort, as well as a cohort of individuals with early dementia, to determine the relative risk of pressure ulcers during periods of prolonged postures and activity.

Aims

The aim of this proof of concept study was to assess the translation of biomarker sampling techniques for the early detection of pressure ulcers in elderly individuals and an early dementia cohort. Specific research questions included:

1. Can methods established for detecting inflammatory biomarkers to identify PUs risk be employed for elderly able-bodied individuals and early dementia individuals?
2. Are there any associations between the biomarkers and the activity levels of able-bodied (young and elderly individuals?
3. Can accelerometers detect activity levels in the elderly dementia population?
4. Do actimetry devices evoke skin irritation?

Materials and Methods

The research protocol was approved by the Ethics committee of the University of Southampton (ERGO 40260). Prior to testing, written informed consent was obtained from all participants classified as young adults (YA) and elderly able-bodied adults (OA) and legal representative of elderly participants with early dementia (DEM).

Study Participants

The study included three distinct cohorts of participants (Table 1). These included: i) Young adults (YA) with ages range 29-53 years and BMI range 22.2-35.2 kg/m^2 recruited from local community. ii) Elderly able bodied (OA) with ages range 60-77 years and BMI range 20.6-28.3 kg/m^2, recruited from local community. iii) Elderly early dementia participants (DEM) with ages range 71-98 years and BMI 17.9-37.8 kg/m^2 recruited from a local care home.

Table 1 Demographic data

Subject Number	Group	Age (years)	Sex	Height (m)	Weight (kg)	BMI (kg/m2)	Comments
1	YA	53	F	1.60	90	35.2	
2	YA	29	F	1.56	63.5	26.1	
3	YA	40	F	1.71	65	22.2	
4	YA	29	M	1.68	74.5	26.4	
5	YA	44	F	1.76	79	25.5	
6	OA	60	F	1.51	62.45	27.4	
7	OA	60	F	1.61	65	25.1	
8	OA	72	M	1.85	70.45	20.6	
9	OA	69	M	1.76	87.6	28.3	
10	OA	61	F	1.64	62.95	23.4	
11	OA	66	F	1.64	62.1	23.1	
12	OA	77	M	1.95	106	27.9	
13	OA	73	F	1.85	70	20.5	
14	DEM	92	F	1.37	49.73	26.5	*Walking frame*
15	DEM	85	F	1.74	92.72	30.6	*Walking stick*
16	DEM	71	F	1.7	51.65	17.9	*Very active (walking the dog everyday)*
17	DEM	93	F	1.62	78.11	29.8	*Walking stick*
18	DEM	98	F	1.24	54.62	35.5	*Walking stick*
19	DEM	88	F	1.4	55.7	28.4	*Imobile*
20	DEM	93	M	1.27	60.96	37.8	*Imobile*

Tests for the YA and OA were performed in the Clinical Academic Facility at Southampton General Hospital where the testing laboratory was controlled at an ambient temperature of 22±1ºC and a relative humidity of 42±6%. Testing in the

DEM cohort was undertaken at a local care home at controlled ambient conditions (23±1ºC and relative humidity of 41±6%) (Green View Residential Care Home, Romsey, Southampton).

Sampling of Inflammatory Biomarkers

Skin markers of inflammation were recovered using a simple and non-invasive absorption method, involving Sebutape® (Fig. 1), which was first described by Perkins, (2001). A range of cytokines and other markers of interest can be determined using specific immunoassays [Perkins, 2001]. Several studies have utilized this method to analyse cytokine levels on healthy and irritated skin [Perkins, 2002; De Jongh, 2007]. The Sebutapes were attached to the skin (Fig. 1) using blunt tweezers and gloved hands, to avoid cross-contamination of skin proteins. After a 2 minute application they were removed and frozen at -80°C prior to biochemical analysis.

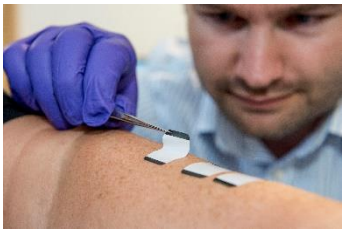


Figure 1. Sebutape® collection method

Biochemical Analysis

The frozen tapes were thawed to room temperature and 2ml of phosphate buffered saline complemented with 0.05% TWEEN (Sigma-Aldrich Co, St. Louis, Missouri, USA) solution added to each vial. After immersion for 1 hour, the tapes were sonicated for 10 minutes at 20± C, vortexed vigorously for 2 minutes, and additionally mixed with a pipette tip. After refreezing overnight at -80°C, the tape extracts were thawed, vortexed for 1 minute and mixed with a pipette to recover the total extracts from the tapes [Perkins, 2001]. Samples from all participants were processed and analysed using Immunoassay kits (ELISA, Peprotech, UK) to estimate concentrations for pro-inflamatory cytokine interleukin 1-alpha (Il-1α). Normalisation was achieved by estimating the ratio between the interleukin concentration over the total amount of protein concentration on each tape extracts (Pierce Coomassie Plus

(Bradford) Assay Kit (Thermo Scientific, USA). The resulting data are expressed as ratio values of post- to pre-loading for cytokine concentrations.

Actimetry

Activity data were collected using a body-worn sensor (Axivity AX3, Axivity Ltd., Newcastle upon Thyme, UK) (Fig. 2) which represented a 3-axis accelerometer, used to monitor movement at a sampling frequency of 100Hz and a sensitivity of ±8g. For activity recognition the accelerometer was mounted on different regions of interests, namely:

i) right hand-using an silicone wrist band that features a cavity on the rear which allows for easy insertion and removal of the sensor and

ii) right ankle- using an elastic band according to the manufacturer specification.

The devices were configured using the standard operating software (Open Movement, OMGUI). The raw signal data was downloaded and the magnitude and duration of activity was estimated using the Signal Vector Magnitude (SVM), calculated using the following equation;

Resultant = [(square root of (x^2+y^2+z^2)].

a) b)

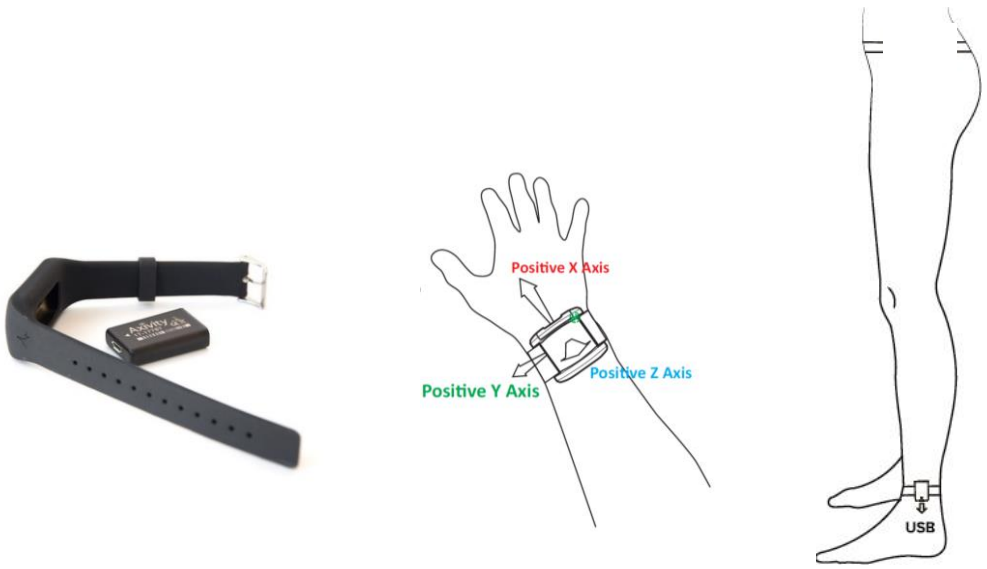


Figure 2. Axivity AX3 accelerometer: a) wrist band; b) mounting position orientation on the right hand and ankle

Protocol:

Biomarkers sampling

A protocol was set up for young and elderly able bodied volunteers that involved lying on a standard hospital mattress for 90 min with change in posture after 30min intervals from (i) supine, (ii) lateral - hip raised at 30° and (iii) high sitting (HS) position with the head of the bed raised to an angle of 40°. This arrangement involved continuous loading of the left side of the sacrum for 90 min, while the right side was loaded in supine (t=0-30min) and HS position (t=60-90min), but unloaded in lateral position (t=30-60min). Measurements of Sebutape samples were collected at the beginning for all sites for baseline (BL), and after every 30min for the right side and after 90min for the left side of the sacrum (Fig. 3).

This protocol had to be adapted for the dementia cohort, as it proved too complex to follow for these individuals, given that it would impact on their daily routine, often involving a nap in a chair. There was also a challenge manoeuvring/moving two of the participants who had limited mobility (wheelchair users). Accordingly, in the case of the dementia cohort, the sacrum of each participant was loaded under their own body weight by resting their back while sitting in a chair. In this case, both sides of the sacrum were continuously loaded for 30 min (Fig.3)

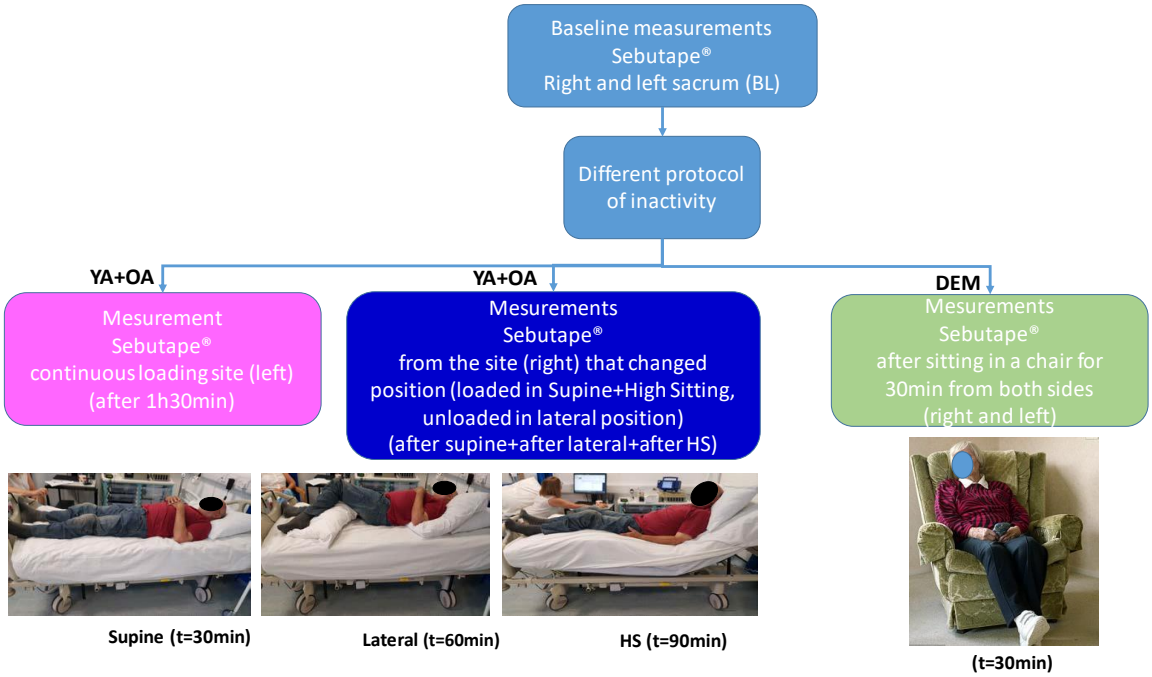


Figure 3. Protocol flow chart for the inactivity session

Actimetry

For the inactivity session, one accelerometer was placed at the wrist. The wristband was secured on the right wrist for short period of time (15min), and for longer periods of time (120min).

For the activity session, involving walking for 5-6 minutes, accelerometers were mounted on two sites, namely the wrist and the ankle (Fig. 4). Two DEM participants were excluded from the activity session (Subject numbers #19 and P20) as they were immobile and bound to a chair.

Figure 4. Image of accelerometer sensors positioned on different body sites: 1) hand and 2) ankle

Results

Biomarkers

RQ1: Can methods for detecting inflammatory biomarkers to identify PUs risk be employed for elderly able-bodied individuals and early dementia individuals?

Concentrations of inflammatory biomarkers were successfully collected from all three cohorts, as summarised in Fig. 5. All of the samples collected from each group were within the limits of detection (8-1000 pg/ml) for the ELISA analysis.

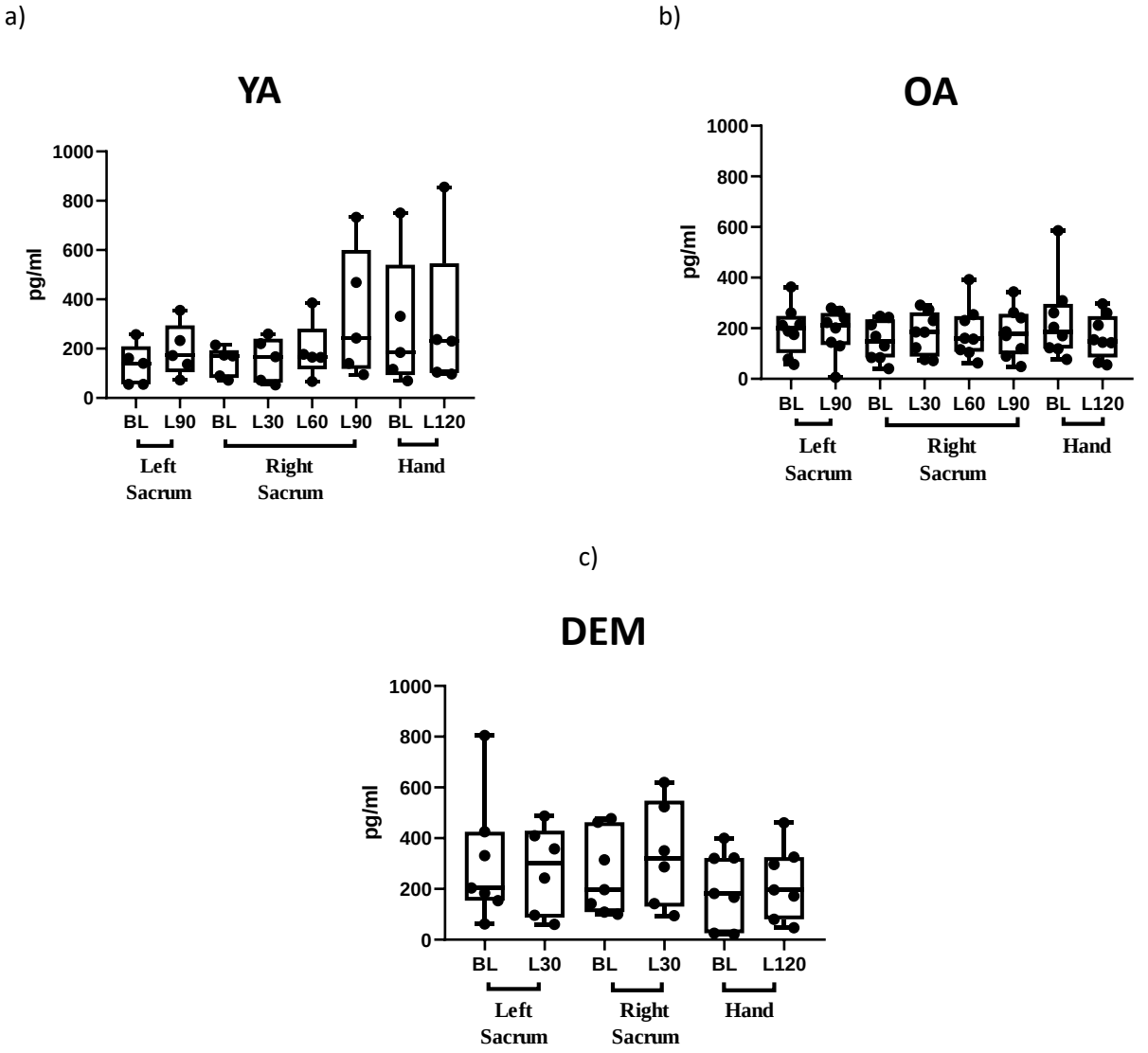


Figure 5. Concentrations of inflammatory biomarker, Il-1α, for early dementia cohort collected from different sites (sacrum and hand) before (BL) and after loading the sacrum (L30, L60, L90) and the hand (L120).

RQ2: Are there any associations between the biomarkers and the activity levels of able-bodies individuals?

There was considerable variance in the inflammatory cytokine concentrations compared to baseline within each cohort (Fig. 6). As an example, participants #1 and #11 exhibited high increases in cytokine ratio for all test conditions. In addition, some participants exhibited differences in response at the right and left sacrum after either lying on the mattress for 90min for YA and OA (4/5 for YA; 5/8 for OA), or sitting

on an armchair for 30min for DEM cohort (2/6). This could be attributed to asymmetry in loading at the sacrum or a difference in local sensitivity to the loading conditions.

The data from the DEM cohort generally revealed ratio values close to unity. The one exception was the response of #16, which revealed a 4-fold increase after 30 minute loading at the right sacrum (Fig. 6c). It should be noted that there is no data for one participant (#20), who fell asleep when samples were to be collected.

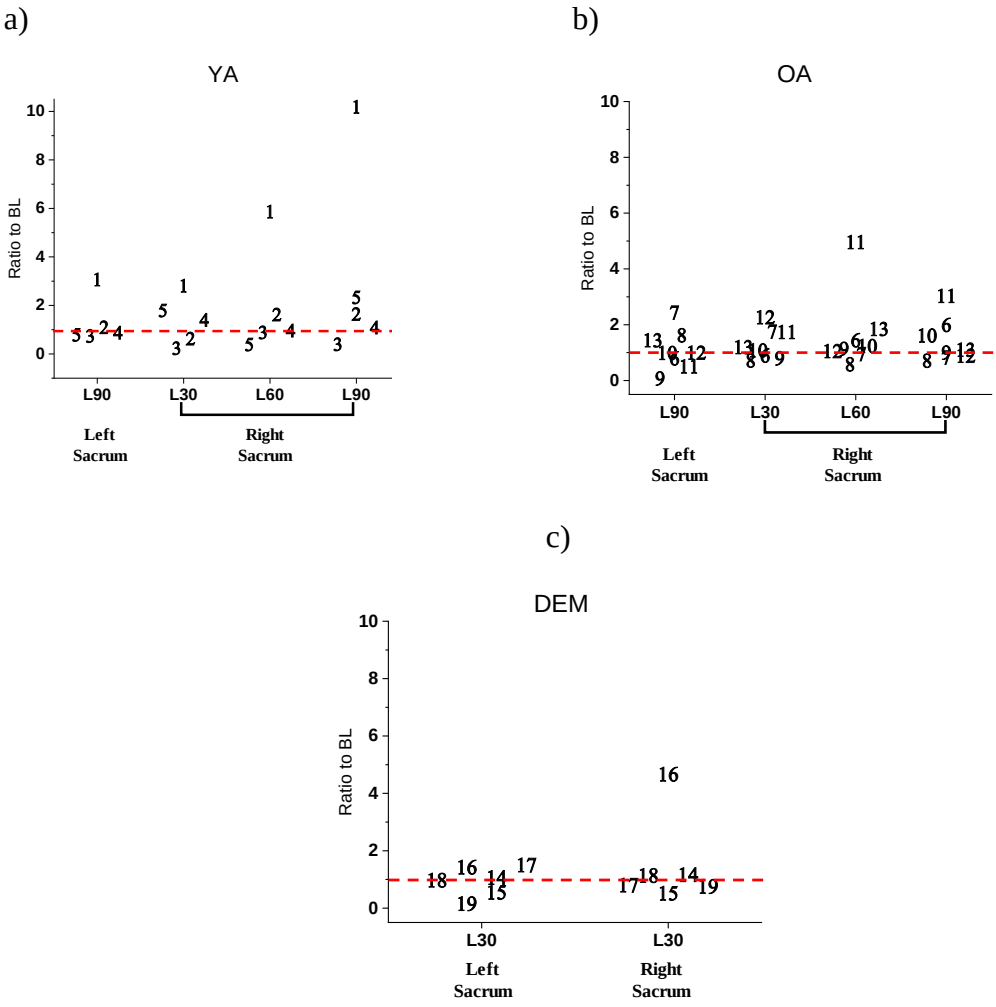


Figure 6. Cluster data of inflammatory biomarker data for a) YA, b) OA and c) DEM cohort. Subject numbers relate to detail in Table 1. Dashed line represents a ratio of 1 i.e. no change from baseline values.

Major findings: The pro-inflammatory biomarkers were successfully sampled non-invasively for the all three groups within the limit of detection. There is generally a difference in inflammation response when the sacral tissues of able-bodied

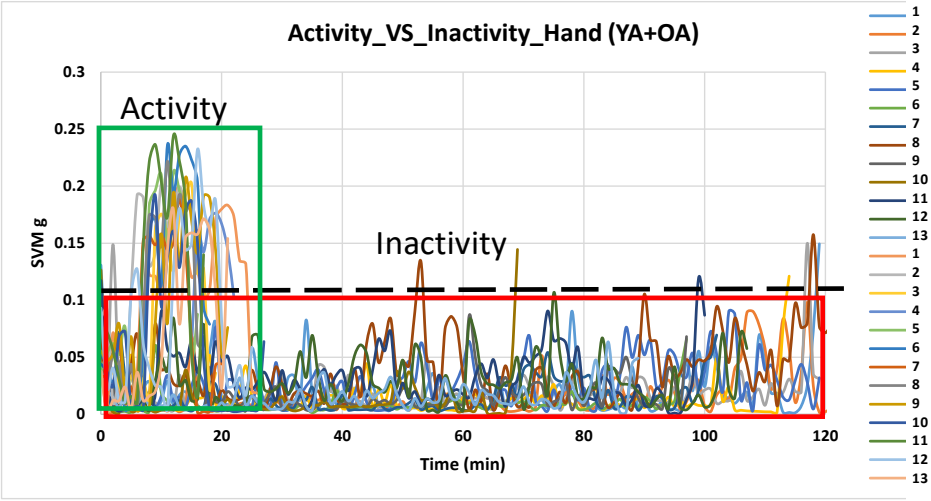
participants are constantly loaded under body weight compared to when they were subjected to regimens of loading and unloading. Although not predicted it appears that, in some cases, the inflammation response with respect to IL-1α, is greater in the case of intermittent loading compared with constant loading (Fig. 6). This finding might be caused by the up-regulation of other cytokines e.g. interleukin 1-receptor antagonist (Il1-RA), which compete directly with Il1-α receptors. Indeed, it has been recently reported that Il1-RA has a compensatory effect in reducing the chemically induced keratinocyte apoptosis [Lee, 2018]. This requires further investigation. It is of note that the protocol required adaptation to accommodate the characteristics/features of the dementia cohort.

Actimetry

RQ3: Can accelerometer sensors detect activity levels in the elderly early dementia population?

Examining the data from the hand sensor for both YA and OA cohorts revealed a threshold level for inactivity of 0.1g . Indeed, during activity the magnitudes at the hand were at least 2.5 times higher than this threshold value (Fig. 7a). By contrast, for the DEM cohort it was more difficult to distinguish between inactivity and activity phases at the hand, with only 1/5 participant demonstrating an increase (~2 fold) in the signal vector magnitude during activity (Fig. 7b).

a)



b)

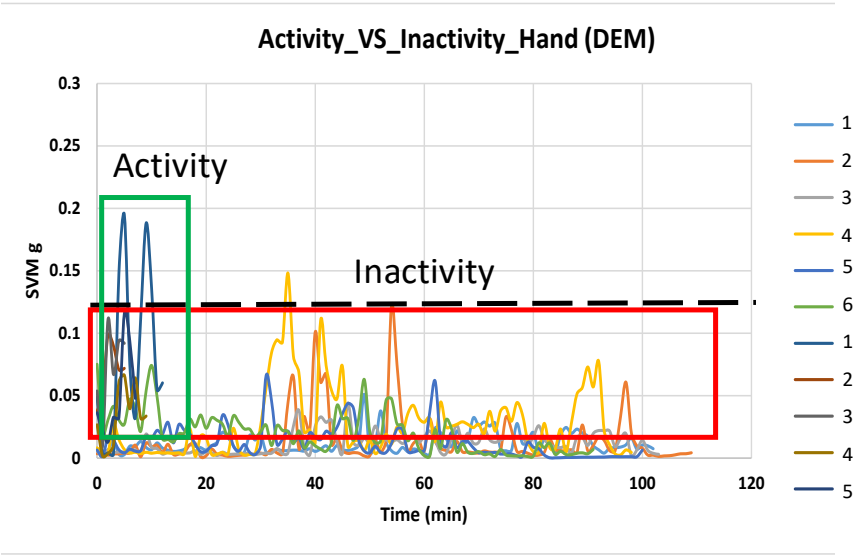


Figure 7. Temporal profiles of SVM for inactivity session compared with activity when the accelerometer is placed at the hand of : a) YA and DEM cohorts; b) DEM cohort.

It was evident that signals from the wrist sensor were inconsistent with the level of activity. As an example, the DEM participant with the walking frame (#14) needed to raise their hands in order to move the frame, with the associated increase in SVM. By contrast, the ankle data reveals little activity due to other co-morbidities (Fig. 8).

Nonetheless, the ankle sensor appears to distinguish the activity levels of the DEM cohort from the other two groups (Fig. 8b). For the DEM participants, the amplitudes of the peaks were smaller and occured less regularly, reflecting the DEM participants moving slower than both YA and OA participants. Therefore, accelerometer mounted at the ankle produced a more accurate representation of the activity levels of participants.

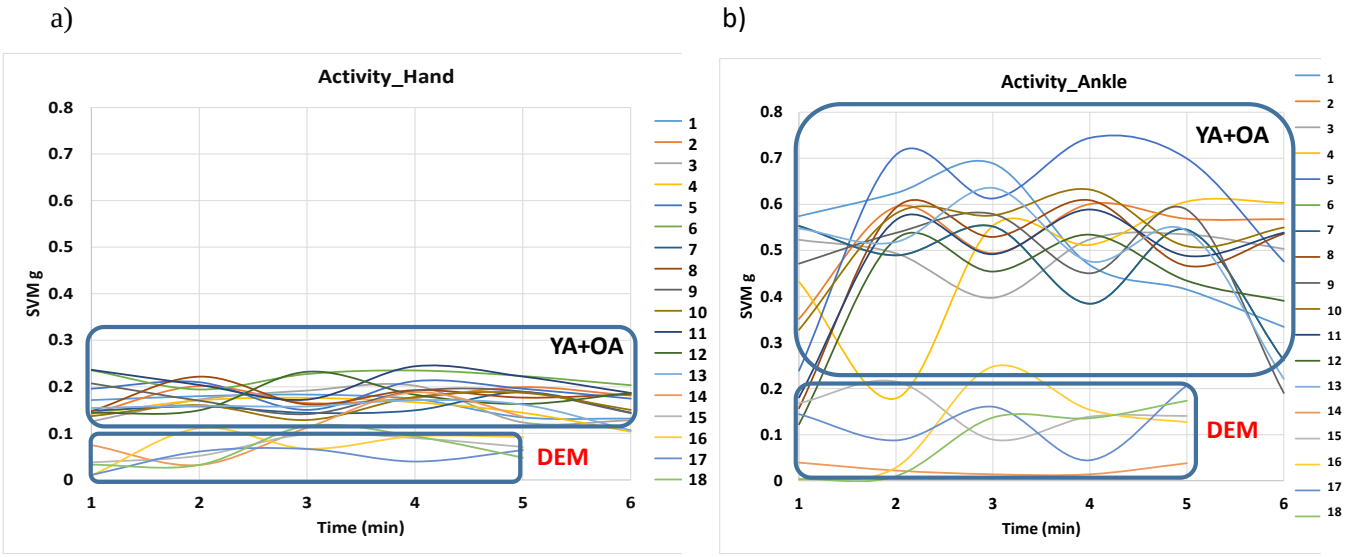


Figure 8. SVM data processed during ambulatory sessions for YA and OA cohorts and DEM cohort when the accelerometers sensors are positioned at the a) wrist and b) ankle

Major findings: Data suggest that there is a clear threshold at 0.1 g when the participants are inactive for the YA and OA participants i.e. resting in bed or lying on a chair). The signal difference was not so evident in the dementia cohort, where the differences between the activity and inactivity were hard to differentiate. Data was more reliable when from the ankle sensor compared to the wrist.

RQ4: Does actimetry devices evoke skin irritation?

Results indicated increased ratios of inflammatory biomarker after extended wearing (120 mins) of the accelerometer at the wrist when compared to short (15 min) wearing periods (Fig. 9). This was more apparent in the DEM cohort (6/7) compared to the YA (3/5) and OA (3/6) cohorts (Fig. 9). Indeed, in many cases of short term wearing, the ratio of the inflammatory marker was equal to or lower than 1.0 (Fig. 9a).

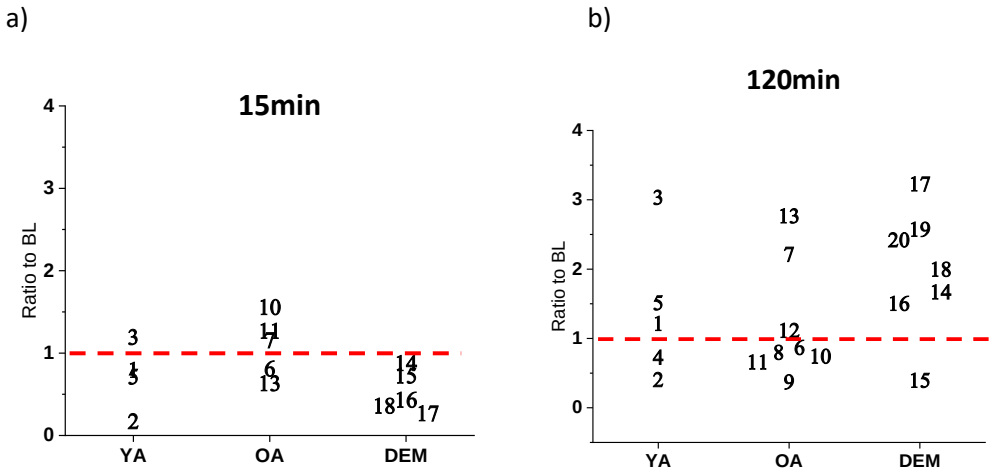


Figure 9. Cluster data of inflammatory biomarker ratios to baseline collected from the hand after wearing the accelerometer sensor for (a) short time or (b) long periods of time.

Discussion

This proof of concept study was designed to evaluate the translation of both biomarker analysis and physical activity monitoring for PU risk in individuals with early dementia. A protocol was established for non-invasive sampling of biomarkers from vulnerable skin sites during periods of prolonged supporting postures. Three cohorts of participants were selected, namely, young and elderly able-bodied participants and a small cohort of early dementia population. It was evident that the test protocol for the dementia cohort needed to be adapted to that from the other cohorts, in order to match their daily routine. The biomarker (Sebutape®) technique was successfully applied to the early dementia cohort.

Activity or inactivity data from accelerometer sensors was collected successfully from early dementia individuals, generally with minimal impact on their daily living. Results indicated the importance of the site to which the sensor was attached in order to reflect the magnitude and level of activity. Indeed, data processing for posture and mobility monitoring was difficult to interpret in the early dementia

cohort, when the sensor was mounted at the hand level. By contrast, for the young and elderly able-bodied participants with a hand-mounted sensor, there was a clear SVM threshold at 0.1g that distinguished inactivity from activity (Fig. 7a). Subsequent results demonstrated that a sensor mounted at the ankle level, provided a more realistic representation of the activity within the DEM cohort (Fig. 8b). This is important as these participants can include a separate walking component, either with a walking stick or walking frame that will result in a higher scalar vector of movement. Thus despite the fact that a sensor is usually mounted on the hand, the present findings imply that an ankle mounting is more appropriate to detect activity levels in early dementia participants.

Future studies are needed to determine the effectiveness of this experimental approach to monitor pressure ulcer risk. This will inevitably involve a range of individuals with mental illness that are at varying risks of developing PUs. The ultimate aim would be to establish an algorithm, based on both biomechanical and biochemical indicators, suitable for early indication of pressure ulcers risk in this vulnerable population.

In conclusion, the combination of technologies can provide a platform for ***an early warning of deteriorating tissue viability,*** providing a means by which timely interventions can be employed. However, more information on the interaction between the wearable devices and the skin status in early dementia individuals is required with particular reference to causing skin irritation.

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