



Association of sedentary time and physical activity during pregnancy with maternal and neonatal labour-related outcomes.

Journal:	<i>Scandinavian Journal of Medicine and Science in Sports</i>
Manuscript ID	Draft
Manuscript Type:	Original Article
Date Submitted by the Author:	n/a
Complete List of Authors:	<p>Baena-García, Laura; Faculty of Health Sciences, University of Granada, Nursery Department Ocón Hernández, Olga; UGC of Gynaecology and Obstetrics, San Cecilio-Campus University Hospital, Granada, Spain Acosta-Manzano, Pedro; University of Granada, Department of Physical Education and Sports, Faculty of Sport Sciences. Coll-Risco, Irene; University of Granada, Department of Physiology, School of Pharmacy, Faculty of Sport Sciences, and Institute of Nutrition and Food Technology Borges-Cosic, Milkana; University of Granada, Department of Physical Education and Sport, Faculty of Sport Sciences Romero, Lidia; School of Medicine. University of Granada, Department of Medical Physiology de la Flor-Aleman, Marta; Department of Physiology, Institute of Nutrition and Food Technology and Biomedical Research Centre, University of Granada, Spain Aparicio, Virginia; University of Granada, Department of Physiology</p>
Keywords:	gestation, accelerometry, umbilical cord blood gas, caesarean section

SCHOLARONE™
Manuscripts

1
2
3 **Association of sedentary time and physical activity during pregnancy with**
4
5 **maternal and neonatal labour-related outcomes.**
6

7 L. Baena, BSc¹, O. Ocón, PhD, MD², P. Acosta, BSc³, I. Coll, BSc⁴, M. Borges., BSc³,
8 L. Romero, BSc³, M. de la Flor, BSc⁴, V. A. Aparicio, PhD⁴
9

10
11 ¹*Department of Nursing, Faculty of Health Sciences, University of Granada, Spain.*

12 ²*UGC of Gynaecology and Obstetrics, San Cecilio-Campus University Hospital,*
13 *Granada, Spain.*
14

15 ³*Department of Physical and Sports Education, Faculty of Sports Science, University of*
16 *Granada, Spain*
17

18 ⁴*Department of Physiology, Institute of Nutrition and Food Technology and Biomedical*
19 *Research Centre, University of Granada, Spain*
20
21

22
23
24 **Corresponding author:** Laura Baena-García, Department of Nursing, Faculty of
25 Health Sciences, University of Granada, Granada, Spain. Plaza Gertrudis Gómez
26 Avellaneda, 48 (Granada), Spain. Telephone number: +34 645211856; **E-mail:**
27 lbaenagarcia@ugr.es
28
29
30
31
32
33

34 **Funding**

35
36 This study was partially funded by the Regional Ministry of Health of the Junta de
37 Andalucía (PI-0395-2016), the Spanish Ministry of Education, Culture and Sport
38 (FPU13/01993; FPU14/02518) and the University of Granada, Unit of Excellence on
39 Exercise and Health (UCEES). This study is included in the thesis of LBG enrolled in
40 the Doctoral Program in Clinical Medicine and Public Health of the University of
41 Granada.
42
43
44
45
46
47
48
49

50 **Conflict of interests:** None of the authors declare any conflict of interests.
51

52
53 **Key words:** gestation; accelerometry; umbilical cord blood gas; caesarean section.
54
55

56 **ABSTRACT**
57
58
59
60

1
2
3 **Aim:** i) To analyse the association of objectively measured sedentary time (ST) and
4 physical activity (PA) during early second trimester of pregnancy with labour-related
5 maternal and neonatal markers; ii) to explore if ST and PA differ between women with
6 vaginal or caesarean section deliveries.
7
8
9

10
11 **Methods:** Ninety-four Caucasian pregnant women (32.9 ± 4.6 years old) participated in
12 this prospective longitudinal study. Triaxial accelerometers were used to assess ST and
13 PA intensity levels for seven consecutive days during second trimester of pregnancy.
14 Labour-related data was collected from the obstetric medical records. Umbilical cord
15 arterial and venous blood gas (pH, partial pressure of carbon dioxide and oxygen, and
16 oxygen saturation) was analyzed after birth.
17
18
19

20
21 **Results:** After adjusting for potential confounders, more ST was associated with higher
22 arterial and venous cord blood partial pressure of carbon dioxide and more acidic
23 arterial and venous pH (all, $p<0.05$). Moderate PA, moderate-to-vigorous PA (MVPA),
24 steps per day and total PA were positively associated with arterial cord blood oxygen
25 saturation (all $p<0.05$). Steps per day were inversely associated with gestational age at
26 delivery ($p<0.01$), duration of first stage of labour and birth weight (all, $p<0.05$). Total
27 and light PA were associated with more alkaline pH in umbilical vein (all, $p<0.05$).
28 Vigorous PA was inversely associated with the Apgar score ($p<0.01$). Women who had
29 caesarean section had expended more time in ST than women who had vaginal
30 deliveries ($p=0.100$).
31
32
33
34
35
36
37
38
39
40
41
42
43
44

45
46 **Conclusion:** Increasing PA and decreasing ST during pregnancy might promote better
47 maternal and neonatal labour-related markers.
48
49
50
51
52
53
54
55
56
57
58
59
60

INTRODUCTION

Uterine blood flow is crucial to meet the nutrient and oxygen requirements of the placenta and the foetus¹. It should be noted that during delivery, uterine contractions induce metabolic stress in the foetus, whose adaptation can be reflected in the umbilical cord blood gases immediately after birth². Actually, small changes of foetal pH could significantly affect the functioning of the cardiovascular system and central nervous system as well as it could be related to worse score in the Apgar test and a higher risk of neonatal complications in short and long term³.

Previously, different types and intensities of physical exercise have been related with the neonatal base acid balance, the foetus-placenta blood flow or the birth weight, among others⁴. To date, it is known that exercise during pregnancy can improve blood perfusion and lower peripheral vascular resistance due to increased angiogenesis, increased endothelial vasodilation⁵ and placental uterine perfusion⁶. However, no studies have previously associated different intensities of physical activity (PA) objectively measured with umbilical cord blood gases and other health-related maternal and foetal parameters. PA is any body movement produced by the skeletal muscles and that produce an energy expenditure higher than basal metabolic rate⁷. The American College of Obstetricians and Gynaecologists (ACOG) recommends at least 150 minutes per week of moderate PA (with daily amounts of 30 minutes or more) for pregnant women without clinical complications⁸. Therefore, it seems possible that PA levels during early second trimester of pregnancy might influence utero-placental perfusion, which could be reflected in the acid-base balance of the neonate as well as ST can have a relevant negative effect on them.

Hence, it is of clinical and social interest to determine whether ST and PA intensity levels are associated with labour-related outcomes for both, the mother and the neonate.

1
2
3 This might guide future studies to focus on specific active lifestyle interventions as new
4 and alternative therapeutic targets in order to avoid adverse labours, including caesarean
5 sections.
6
7
8
9

10 Therefore, the aims of the present study were: i) To explore the association of
11 objectively measured ST and PA levels during early second trimester of pregnancy with
12 labour-related maternal and neonatal markers; ii) to investigate if ST and different PA
13 intensity levels during early second trimester of pregnancy differ between women with
14 vaginal or caesarean section deliveries.
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

PROOF

METHODS

Study design and participants

This study is part of the GESTation and FITness (GESTAFIT) project, and its complete methodology as well as inclusion-exclusion criteria (**Table S1**) can be found elsewhere⁹. From the 229 women contacted at “San Cecilio” Hospital in Granada (southern Spain) we recruited 161 pregnant women (**Figure S1**). Clinical Research Ethics Committee of Granada, Government of Andalusia, Spain (code: GESFIT-0448-N-15) approved this study. A written informed consent was signed by the participants before beginning the study.

Procedures

After being contacted from the research team in their first gynecologist visit to the Hospital in their 12th gestational week, participants were invited to carry on the study at “Instituto Mixto Universitario Deporte y Salud”, University of Granada. In 16th gestational week, a first measurement was carried out. In this evaluation, an initial survey (anamnesis) was performed in order to compile information on the sociodemographic and clinical characteristics.

Measurements

Sociodemographic and clinical data

The collection of sociodemographic (such as number of children, educational level or marital status), reproductive history, and clinical data (hypertension, diabetes, obesity, etc.) was done through a self-reported survey by the participants. The researchers explained how to fill out this questionnaire properly. This information was gathered by means of an auto administered questionnaire, which also included questions about smoking or alcohol habit and indicators of the socioeconomic status. In addition,

1
2
3 information about the obstetric history of the pregnant woman, such as the evolution of
4
5 previous pregnancies and data related to the current gestation were collected. After
6
7 delivery, data regarding the onset of labour (spontaneous or induced), type of analgesia
8
9 employed (if any), duration of first and second stage of labour, expulsion of meconium,
10
11 arterial and venous umbilical cord blood gas analysis and Apgar score in the newborn
12
13 were collected from medical records. The Apgar test is used to assess the status of the
14
15 newborn. In this way, the heart rate, respiratory effort, muscle tone, skin color, and
16
17 reflex irritability are evaluated. It is done at one and five minutes after birth and the
18
19 maximum score is 10, which means that the newborn is in the best conditions.
20
21

22 ***Obstetric History***

23
24 Obstetric and gynecological histories were collected through the “Pregnancy Health
25
26 Document”, which is a document provided to all pregnant women by the Andalusian
27
28 regional government where data related to the health check-ups are periodically
29
30 recorded. Hence, information regarding the number and evolution of previous
31
32 pregnancies, gynecological antecedents and previous births, was obtained from this
33
34 document. Gestational age was calculated from the date of last menstruation corrected
35
36 for cycles of 28 days, and subsequently corrected, if needed, by ultrasound.
37
38

39 ***Maternal anthropometry and body composition***

40
41 Maternal baseline height was measured with a stadiometer (Seca22, Hamburg) and body
42
43 weight was measured in the 16th gestational week with a scale (InBody R20, Biospace,
44
45 Seoul, Korea). Body mass index (BMI) was calculated as weight (kg) divided by height
46
47 (m) squared.
48
49

50 ***Sedentary time and physical activity intensity levels***

51
52 ST and PA were objectively assessed with triaxial accelerometry (ActiGraph GT3X+,
53
54 Pensacola, Florida, US), using an epoch length of 60 seconds and a frequency rate of 30
55
56
57
58
59
60

1
2
3 Hz. The pregnant women carried the accelerometer around the hip 24 hours per day for
4
5 9 consecutive days. A total of 7 days of recording with a minimum registration
6
7 of ≥ 10 hours/day was necessary to be included in the study. The hours of sleep and those
8
9 in which they did not wear the accelerometer were subtracted from the total registered
10
11 time for the whole day (usually 1.440 min) obtaining “accelerometer wearing time”.
12
13 Values with recording of $\geq 20,000$ counts/min were excluded because of potential
14
15 malfunction. Bouts of 90 continuous minutes of 0 activity intensity counts were also
16
17 excluded from the analyses.
18

19
20 Accumulated time below 200 counts per minute (minimum periods of 10 minutes) was
21
22 used to calculate ST, and it was expressed in minutes per day¹⁰. The time involved
23
24 in PA intensity levels (light, moderate, moderate-to-vigorous and vigorous) were
25
26 calculated based on recommended PA vector magnitude cut points ≥ 200 -2690, ≥ 2690 -
27
28 6166, ≥ 2690 and ≥ 6167 counts/min¹¹, respectively, and were expressed in min/day. The
29
30 minutes of moderate-to-vigorous physical activity (MVPA) bouts per week were also
31
32 calculated. Bouted MVPA was defined as a period of ≥ 10 consecutive minutes spent in
33
34 that behaviour (up to 2 minutes below the cut point allowance). Groups of meeting PA
35
36 guidelines were established according to the PA recommendations for adults: not
37
38 meeting PA recommendations (< 150 min/week of bouted MVPA) and meeting PA
39
40 recommendations (≥ 150 min/week of bouted MVPA). Data download, reduction,
41
42 cleaning, and analyses were performed using ActiGraph software (ActiLife v. 6.13.3).
43
44 In the first assessment, a PA diary was given to participants to register activities that the
45
46 accelerometer cannot record, such as swimming or cycling.
47
48
49

50 ***Labour-related outcomes***

51
52 After delivery, we collected information about parity, gestational age at delivery, type
53
54 of labour onset (spontaneous, induced or stimulated by oxytocin or prostaglandins),
55
56
57
58
59

1
2
3 moment of rupture of the amniotic sac and duration of the first and second stages of
4 labour. Currently, there is little consensus about when the active phase or first stage of
5 labour begins¹². The duration of the first stage was defined as the period comprising a
6 cervical dilatation of 4 centimeters or more with regular uterine contractions until full
7 dilatation, which was defined by a dilatation of the cervix of 10 centimeters. The second
8 stage of labour or expulsive period occurs between complete dilatation of the uterine
9 cervix and complete delivery of the foetus. Likewise, after delivery of the newborn, we
10 collected information about the type of delivery (eutocic, instrumental or caesarean
11 section).

22 ***Umbilical cord blood gas***

23
24 Samples of arterial and venous blood from the umbilical cord were collected before the
25 delivery of the placenta to assess pH, partial pressure of carbon dioxide (PCO₂), partial
26 pressure of oxygen (PO₂) and oxygen saturation using a blood analyzer (GEM Premier
27 4000). Double clamping of the umbilical cord is performed by a trained midwife
28 between the first and third minutes life of the neonate, with a minimum distance
29 between both clamps of 10 centimeters. For the extraction of blood, pre-heparinized
30 1mL syringe is used. The gas analysis is carried out at the time of extraction at room
31 temperature¹³.

42 **Statistical analysis**

43
44 Descriptive statistics (mean (standard deviation) or number (%)) were employed to
45 show the socio-demographic, clinical characteristics and levels of objectively measured
46 PA of the study sample. The association of MVPA with ST and PA levels with labour-
47 related maternal and neonatal markers was assessed with partial correlations after
48 adjusting for maternal age, parity, BMI and accelerometer wearing time. An analysis of
49 the covariance (ANCOVA) after adjustment for the above mentioned potential
50
51
52
53
54
55
56
57
58
59
60

1
2
3 confounders was employed to explore the differences in ST and PA levels between
4 women who had vaginal deliveries (eutocics and instrumentals) versus caesarean
5 section. Additionally, standardized effect size statistics were estimated in all the
6 comparisons through Cohen's d and its exact confidence interval. The exact confidence
7 intervals for Cohen's d were obtained by means of the non-centrality parameter of the
8 non-central Student's distribution using Wolfram-Mathematica 8.0. The effect size was
9 interpreted as small (~ 0.25), medium (~ 0.5) or large (~ 0.8 or greater). Finally, such as in
10 the GESTAFIT project, a concurrent physical exercise program was carried out, we
11 have also adjusted all the models for the exercise intervention (control or intervention).
12
13 The statistical analyses were performed with SPSS (IBM SPSS Statistics for Windows,
14 version 20.0; Armonk, NY, USA) and the statistical significance was set at $\alpha=0.05$.
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

RESULTS

From all the participants who met the eligibility criteria, 161 were cited for the first assessment and 94 Caucasian pregnant women (age 32.9 ± 4.6 years old, BMI $24.9 \pm 4.1 \text{ kg/m}^2$) accepted to participate and presented valid data for the present analyses.

The flowchart of the participants for this specific study aims is shown in Figure S1.

The sociodemographic and clinical characteristics of the study participants are shown in Table 1. Fifty-four percent of the participants had University studies and half of the sample worked full-time (47%). Regarding the type of delivery, 61% of the women had eutocic deliveries, 15% had instrumental deliveries and 24% had caesarean section. The deliveries took place around 39.7 ± 1.2 week of gestation, with a mean neonate body weight at birth of 3310 ± 468.3 grams. Mean Apgar test score at the first minute of life was 8.7 ± 0.9 . Participants spend around 3598 ± 682.4 minutes per week in sedentary time, and 95 ± 115.2 minutes per week in MVPA in bouts of at least 10 minutes.

Pearson's partial correlations of ST and PA levels during early second trimester of pregnancy with labour-related maternal and neonatal markers are shown in Table 2.

After adjusting for maternal age, parity, BMI, accelerometer wearing time and the exercise intervention, ST was associated with a more acidic arterial ($r = -0.262$, $p < 0.05$) and venous ($r = -0.267$, $p < 0.05$) cord blood pH and higher arterial ($r = 0.335$, $p < 0.01$) and venous ($r = -0.299$, $p < 0.01$) cord blood partial pressure of carbon dioxide.

Higher levels of light PA were associated with less acidic venous cord blood pH concentrations ($r = 0.251$, $p < 0.05$). Moderate and bouted MVPA were positively associated with arterial oxygen saturation ($r = 0.251$, $p < 0.05$ and $r = 0.266$, $p < 0.05$, respectively) as well as moderate PA ($r = 0.251$, $p < 0.05$) and greater total PA ($r = 0.263$, $p < 0.05$), which is also associated with less acidic venous cord blood pH

1
2
3 (r=0.264, $p<0.05$). Nevertheless vigorous PA levels were inversely associated with
4
5 the Apgar test at first minute (r=-0.365, $p<0.01$), and at five minutes (r=-0.342,
6
7 $p<0.01$) of life. Finally, steps per day were associated with lower length of the first
8
9 stage of labour (r=-0.274, $p<0.05$), lower neonate body weight (r=-0.208, $p<0.05$)
10
11 and greater arterial cord blood oxygen saturation (r=0.318, $p<0.05$).

12
13 Differences on ST and PA levels of the study participants by delivery mode (vaginal or
14
15 caesarean section) are shown in Table 3. A borderline significant difference was
16
17 observed in ST between women who had caesarean sections and those who had vaginal
18
19 deliveries (mean difference with 95%CI, $p=0.091$ for the unadjusted model and $p=0.112$
20
21 for the adjusted model; Cohen's $d=0.39$). Women who had caesarean sections spent less
22
23 minutes on PA, regardless of the intensity level: light PA (mean difference with 95% CI
24
25 $p=0.088$ for the unadjusted model and $p=0.223$ for the adjusted model, Cohen's
26
27 $d=0.29$), Moderate PA (mean difference with 95% CI $p=0.695$ for the unadjusted model
28
29 and $p=0.605$ for the adjusted model, Cohen's $d=0.12$), vigorous PA (mean difference
30
31 with 95% CI $p=0.046$ for unadjusted model and $p=0.269$ for the adjusted model,
32
33 Cohen's $d=0.26$) and MVPA (mean difference with 95% CI $p=0.489$ for the unadjusted
34
35 model and $p=0.315$ for the adjusted model, Cohen's $d=0.24$). In addition, women who
36
37 had caesarean section had less weekly total PA than those who had a vaginal delivery
38
39 (mean difference with 95% CI $p=0.073$ for the unadjusted model and $p=0.189$ for the
40
41 adjusted model , Cohen's $d=0.31$)
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

DISCUSSION

As far as we know, this is the first study exploring the association of objectively measured ST and PA intensity levels during early second trimester of pregnancy with labour-related health markers of the mother and foetus. A major finding of the present study is that more ST is associated with a lower pH as well as higher partial pressure of carbon dioxide in both umbilical artery and vein. Likewise, higher levels of total, moderate, MVPA and steps per day are associated with greater umbilical arterial oxygen saturation, and greater total and light PA are related to higher levels of venous cord blood pH. It is also noteworthy that women who had caesarean presented more ST during early second trimester of pregnancy.

Association of ST and PA levels with labour-related outcomes

We found that greater number of steps per day were associated with shorter duration of the first stage of labour, lower gestational age and weight at birth, and better oxygen saturation in the umbilical artery. A lower weight of the newborn influences the reduction of the time of the first stage of delivery, as other studies have previously shown¹⁴. Avoiding a prolonged duration of the first stage of labour is important, since it has been associated with more obstetric interventions, instrumented deliveries, and caesareans sections¹⁵. In addition, the shorter time of cervical dilatation might have influenced the better saturation of oxygen in the umbilical artery after delivery, which is a positive sign of foetal well-being, since uterine contractions during labour produce acute restrictions of blood flow from the placenta to the fetus². A lower neonate weight might be related to lower gestational age¹⁶. In fact, when this correlation is adjusted for gestational age at labour, the steps per day are not linked with the newborn weight. However, taking into account that both, the age and weight of the newborn were within normal parameters, the reduction of these parameters could be interpreted as positive

1
2
3 effects¹⁷. Indeed, foetal macrosomia has been associated with increased risk of
4 caesarean section, shoulder dystocia and longer duration of the first stage of labour,
5 among others¹⁸. Findings regarding the associations of steps per day with the labour
6 length cannot be commented with regard to other studies, since it has never been
7 explored in pregnant women. It is possible that women who walked more during second
8 trimester of pregnancy, were more active during late pregnancy too. Hence, since
9 aerobic exercise performed regularly during pregnancy shortens the first phase of
10 labour¹⁹, a plausible explanation could be that PA, which is a similar stimulus to aerobic
11 walking, even at low intensity²⁰, might influence the shortening of the first stage of
12 labour.
13
14
15
16
17
18
19
20
21
22
23

24 *Association of ST and PA levels with neonate-related outcomes*

25
26 In agreement with our results, Ruifrok et al.²¹ observed that objectively measured ST
27 was not associated with gestational age or birth weight. We also observed that greater
28 ST during early second trimester pregnancy was associated with higher arterial partial
29 pressure of carbon dioxide (PCO₂), and more acidic pH in both arterial and venous cord
30 blood. This is a relevant finding because umbilical arterial cord blood gas at birth is a
31 gold standard in the determination of the acid-base balance in the foetus²².
32 Consequently, measuring PCO₂ in the umbilical cord blood is useful to identify foetal
33 acidosis²³. Rate of CO₂ production is proportional to foetal oxygen consumption²⁴ and
34 the higher cord blood PCO₂ and decrease in pH indicate a state of foetal acidosis². If
35 this acidosis is reflected exclusively in the umbilical artery, it would be a consequence
36 of the own labour, or other acute situations, and usually affects only peripheral tissues²⁵.
37 However, venous umbilical cord blood gas indicates the state of the placenta, so that
38 increases of PCO₂ and decreases of pH could be related to a chronic decrease in blood
39 flow, probably from the mother to the placenta²⁶. Therefore, our results suggest that
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 higher ST might be related with increased foetal acidosis during delivery, which may be
4
5 indicative of a worse placental perfusion^{3,6}.

6
7 Otherwise, in this study, vigorous PA has been associated with a worse score in the
8
9 Apgar test at one and five minutes of life. Apgar test has been shown to be effective on
10
11 predicting neonatal morbidity and mortality in term babies with normal birth weight²⁷.
12
13 Low scores in the Apgar test have also been related to dysfunctions in cognitive
14
15 ability²⁸. This finding requires further studies and should be taken into account by
16
17 health professionals in the counselling and monitoring of pregnant women.

18
19 Results regarding the positive associations found between total and bouts MVPA with
20
21 neonatal outcomes suggest that the practice of total PA or MVPA may have beneficial
22
23 influence on the newborn. Currently, more studies are needed to explore which specific
24
25 maternal factors, including sedentary behaviours and PA, could influence placental
26
27 blood flow. However, several studies suggest that regular exercise during pregnancy
28
29 increases placental growth and its ability to perfuse oxygen and nutrients to the foetus²⁹.
30
31 These statements are consistent with our findings, in which oxygen saturation was better
32
33 in women with greater low to moderate PA levels, perhaps because increasing PA has a
34
35 similar effect on placental angiogenesis during early pregnancy. The increase in PA
36
37 intensity (which indirectly represents the muscle mass involved in the contractile
38
39 activity, such as increased aerobic exercise intensity) might lead to a generally transient
40
41 reduction of uterine-placental blood flow, which could overcome the compensatory
42
43 mechanisms of the placenta³⁰. This could have influenced the lower score in the Apgar
44
45 test observed in those newborns whose mothers performed more minutes of vigorous
46
47 PA. Other studies have previously evaluated the association of PA with other neonatal
48
49 parameters, such as birth weight³¹. However, more studies are needed to analyze the
50
51
52
53
54
55
56
57
58
59
60

1
2
3 association of vigorous PA with the Apgar test score for a better understanding of these
4
5 results.

6
7 Finally, findings observed in relation to ST and PA levels among different types of
8
9 delivery (i.e. caesarean or vaginal) need to be highlighted. The fact that women who had
10
11 a caesarean section had expended, overall, more ST and less time in total PA is of
12
13 clinical and social relevance. Our results agree with those described by Nielsen et al.³²
14
15 who found a decrease in the rate of caesarean sections in women who had greater PA
16
17 levels during the first and second trimesters of pregnancy. These results could be
18
19 explained by an improvement in placental function in exercised pregnant women⁶.
20
21 Indeed, the study carried out by Jackson et al.³³ found that PA during mid pregnancy
22
23 increased the parenchymal component of the placenta as well as capillary and total
24
25 vascular volumes. Moreover, our results suggest that neonates of more active women
26
27 have a better acid-base balance, which might reduce the risk of caesarean section due to
28
29 loss of foetal well-being.
30
31

32
33 It should be noted that 24.5% of births in the present study occurred by caesarean
34
35 section, which is similar to the rate described in the pregnant population of the same
36
37 geographical area³⁴. However, the World Health Organization establishes that caesarean
38
39 rates above 10% are not associated with a reduction in maternal or neonatal morbidity
40
41 and mortality³⁵, so its abuse is not clinically justified. This is clinically relevant because
42
43 caesarean incidence rates in Spain are extremely high, which implies greater health
44
45 costs and risk for both, the mother and the newborn^{36,37}. In a study carried out in
46
47 Canada, a saving of \$27 million, in just four years, was achieved by implementing a
48
49 program aimed at reducing caesarean sections³⁸. Taking also into account that only a
50
51 quarter of the women who participated in the present study met PA recommendations,
52
53
54
55
56
57
58
59
60

1
2
3 we may considerate that there is still a large room for behavioural changes in order to
4
5 improve maternal and newborn labour-related markers.

6 7 *Limitations and strengths*

8
9 This study presents several limitations that must be underlined. Firstly, the cross-
10
11 sectional design precludes determination of causality. Secondly, the results should be
12
13 interpreted with caution due to the small size of the sample, and is advisable to recruit a
14
15 greater number of pregnant women to render the obtained results statistically more
16
17 relevance. Third, accelerometry does not register activities such as biking or swimming,
18
19 but pregnant women did not report to practice these activities in their personal PA
20
21 notebook. This study has also several strengths. Firstly, to the best of our knowledge,
22
23 this is the first study providing a comprehensive examination of the association of
24
25 objectively measured ST and PA during early second trimester of pregnancy with
26
27 maternal and foetal relevant labour-related outcomes. Secondly, the measurement of
28
29 gases in the artery umbilical cord blood is a gold standard in the determination of the
30
31 acid-base status in the foetus. Thirdly, paired samples have been taken (venous and
32
33 arterial blood) that allow a better interpretation of the results. Fourthly, the analysis of
34
35 different PA intensities (including vigorous PA levels) is a strength, since it has
36
37 previously been pointed out that the analysis of vigorous PA together with moderate PA
38
39 could mask the true effects of a higher PA intensity³⁹. Finally, our measurement tool to
40
41 objectively assess ST and PA intensity levels (i.e. triaxial accelerometry) is widely valid
42
43 and reliable, if not the gold standard.

44 45 46 47 **CONCLUSION**

48
49 Overall, in this population of pregnant women at low-risk, we found that the greater
50
51 levels of light, moderate, moderate-to-vigorous, and total PA as well as steps per day,
52
53 during early second trimester of pregnancy, were associated with better labour-related
54
55
56
57
58
59
60

1
2
3 maternal and neonatal markers. Contrary, ST and vigorous PA could have harmful
4
5 influence on labour-related outcomes on both, the mother and the newborn.
6
7

8 **PERSPECTIVES**

9
10 The findings of the present study might be considered relevant for the clinical practice.
11
12 Our results contribute to a better understanding of the associations between PA and
13
14 labour related outcomes, both in the mother and the newborn. Consequently, increasing
15
16 PA and decreasing ST could be also useful obstetric tools. More studies, performed in
17
18 different populations of pregnant women and in greater sample sizes, are needed to
19
20 confirm or contrast the present findings. Moreover, future research is warranted to
21
22 explore whether intervention based on increasing PA or decreasing ST during
23
24 pregnancy improve these labour-related outcomes.
25
26
27

28 **ACKNOWLEDGEMENTS**

29
30
31 For financial support, we thank the Regional Ministry of Health of the Junta de
32
33 Andalucía, the Spanish Ministry of Education, Culture and Sport and the University of
34
35 Granada, Unit of Excellence on Exercise and Health.
36
37
38

39 **REFERENCES**

- 40
41
42 1. Mayhew TM, Charnock-Jones DS, Kaufmann P. Aspects of human fetoplacental
43
44 vasculogenesis and angiogenesis. III. Changes in complicated pregnancies.
45
46 *Placenta*. 2004;25(2-3):127-139. doi:10.1016/j.placenta.2003.10.010.
47
48
49 2. Armstrong L, Stenson BJ. Use of umbilical cord blood gas analysis in the
50
51 assessment of the newborn. *Arch Dis Child Fetal Neonatal Ed*. 2007;92(6).
52
53 doi:10.1136/adc.2006.099846.
54
55
56
57
58
59
60

- 1
2
3 3. Omo-Aghoja L. Maternal and fetal acid-base chemistry: A major determinant of
4 perinatal outcome. *Ann Med Health Sci Res*. 2014;4(1):8. doi:10.4103/2141-
5 9248.126602.
6
7
8
- 9
10 4. Clapp JF. The effects of maternal exercise on fetal oxygenation and fetoplacental
11 growth. In: *European Journal of Obstetrics Gynecology and Reproductive Biology*. ; 2003. doi:10.1016/S0301-2115(03)00176-3.
12
13
14
15
- 16
17 5. Schuler G, Adams V, Goto Y. Role of exercise in the prevention of
18 cardiovascular disease: Results, mechanisms, and new perspectives. *Eur Heart J*.
19 2013;34(24):1790-1799. doi:10.1093/eurheartj/eh111.
20
21
22
23
- 24 6. Reyes LM, Davenport MH. Exercise as a therapeutic intervention to optimize
25 fetal weight. *Pharmacol Res*. 2018;132(April):160-167.
26
27 doi:10.1016/j.phrs.2018.04.016.
28
29
30
- 31 7. Brubaker P, Otto R, Whaley M. American College of Sports Medicine: ACSM's
32 guidelines for exercise testing and prescription. *Am Coll Sport Med*. 2006.
33
34
35
36
- 37 8. American College of Obstetricians and Gynecologists. ACOG Committee
38 Opinion No. 650: Physical Activity and Exercise During Pregnancy and the
39 Postpartum Period. *Obs Gynecol*. 2015;126(6):e135-e142.
40
41
42
43
44
45
46
- 47 9. Aparicio VA, Ocón O, Padilla-Vinuesa C, Soriano-Maldonado A, Romero-
48 Gallardo L, Borges-Cóscic M, Coll-Risco I, Ruiz-Cabello P, Acosta-Manzano P,
49 Estévez-López F, Álvarez-Gallardo IC, Delgado-Fernández M, Ruiz JR, Van
50 Poppel MN, Ochoa-Herrera JJ. Effects of supervised aerobic and strength
51 training in overweight and grade I obese pregnant women on maternal and foetal
52
53
54
55
56
57
58
59
60

- 1
2
3 health markers: the GESTAFIT randomized controlled trial. *BMC Pregnancy*
4 *Childbirth*. 2016;16(1):290. doi:10.1186/s12884-016-1081-y.
5
6
7
8 10. Aguilar-Farías N, Brown WJ, Peeters GMEEG. ActiGraph GT3X+ cut-points for
9 identifying sedentary behaviour in older adults in free-living environments. *J Sci*
10 *Med Sport*. 2014;17(3):293-299. doi:10.1016/j.jsams.2013.07.002.
11
12
13
14
15 11. Sasaki JE, John D, Freedson PS. Validation and comparison of ActiGraph
16 activity monitors. *J Sci Med Sport*. 2011;14(5):411-416.
17
18
19
20
21
22
23 12. Hanley GE, Munro S, Greyson D, Gross MM, Hundley V, Spiby H, Janssen PA.
24 Diagnosing onset of labor: A systematic review of definitions in the research
25 literature. *BMC Pregnancy Childbirth*. 2016;16(1). doi:10.1186/s12884-016-
26
27
28
29
30
31
32 13. Butterwegge M, Kappen R, Rath W. [Changes in umbilical cord blood acid-base
33 status after delivery in dependence on time intervall--a continuing forensic
34 problem]. *Z Geburtshilfe Neonatol*. 2012;216(6):253-258. doi:10.1055/s-0032-
35
36
37
38
39
40
41
42 14. Gunnarsson B, Skogvoll E, Jónsdóttir IH, Røislien J, Smáráson AK. On
43 predicting time to completion for the first stage of spontaneous labor at term in
44 multiparous women. *BMC Pregnancy Childbirth*. 2017;17(1).
45
46
47
48
49
50
51 15. Ängeby K, Wilde-Larsson B, Hildingsson I, Sandin-Bojö A-K. Prevalence of
52 Prolonged Latent Phase and Labor Outcomes: Review of Birth Records in a
53 Swedish Population. *J Midwifery Womens Health*. 2018;63(1):33-44.
54
55
56
57
58
59
60

- 1
2
3 doi:10.1111/jmwh.12704.
4
5
6 16. Mikolajczyk RT, Zhang J, Betran AP, Souza JP, Mori R, Gülmezoglu AM,
7 Merialdi M. A global reference for fetal-weight and birthweight percentiles.
8 *Lancet*. 2011;377(9780):1855-1861. doi:10.1016/S0140-6736(11)60364-4.
9
10
11
12
13 17. Bisson M, Croteau J, Guinhouya BC, Bujold E, Audibert F, Fraser WD, Marc I.
14 Physical activity during pregnancy and infant's birth weight: results from the 3D
15 Birth Cohort. *BMJ Open Sport Exerc Med*. 2017;3(1):e000242.
16
17
18
19
20
21
22
23 18. Walsh J, Hehir M, Robson M, Mahony R. Mode of delivery and outcomes by
24 birth weight among spontaneous and induced singleton cephalic nulliparous
25 labors. *Int J Gynecol Obs*. 2014;dx.doi.org:22-25.
26
27
28
29
30 19. Barakat R, Franco E, Perales M, López C, Mottola MF. Exercise during
31 pregnancy is associated with a shorter duration of labor. A randomized clinical
32 trial. *Eur J Obstet Gynecol Reprod Biol*. 2018. doi:10.1016/j.ejogrb.2018.03.009.
33
34
35
36
37 20. Ruchat SM, Davenport MH, Giroux I, Hillier M, Batada A, Sopper MM,
38 Hammond JA, Mottola M. Walking program of low or vigorous intensity during
39 pregnancy confers an aerobic benefit. *Int J Sports Med*. 2012. doi:10.1055/s-
40 0032-1304635.
41
42
43
44
45
46 21. Ruifrok AE, Althuisen E, Oostdam N, Van Mechelen W, Mol BW, De Groot
47 CJM, Van Poppel MNM. The relationship of objectively measured physical
48 activity and sedentary behaviour with gestational weight gain and birth weight. *J*
49 *Pregnancy*. 2014;2014. doi:10.1155/2014/567379.
50
51
52
53
54
55
56 22. Thorp JA, Rushing RS. UMBILICAL CORD BLOOD GAS ANALYSIS. *Obstet*
57
58
59
60

- 1
2
3 *Gynecol Clin North Am.* 1999;26(4):695-709.
4
5 doi:http://dx.doi.org/10.1016/S0889-8545(05)70107-8.
6
7
- 8 23. Neonatal Professional Committee of Chinese Medical Doctor Association.
9
10 [Experts' consensus on the criteria for the diagnosis and grading of neonatal
11 asphyxia in China]. *Zhongguo Dang Dai Er Ke Za Zhi.* 2013;15(1):1.
12
13 doi:10.7499/j.issn.1008-8830.2013.01.002.
14
15
- 16
17 24. Blechner JN. Maternal-fetal acid-base physiology. *Clin Obstet Gynecol.*
18
19 1993;36(1):3-12. doi:10.1097/00003081-199303000-00004.
20
21
- 22 25. Hagelin A, Leyon J. The effect of labor on the acid-base status of the newborn.
23
24 *Acta Obstet Gynecol Scand.* 1998;77(8):841-844. doi:10.1080/j.1600-
25
26 0412.1998.770810.x.
27
28
- 29 26. Johnson JWC, Richards DS, Cook WA, Hopwood HG, Devoe LD. The etiology
30
31 of fetal acidosis as determined by umbilical cord acid- base studies. In: *American*
32
33 *Journal of Obstetrics and Gynecology.* Vol 177. ; 1997:274-282.
34
35 doi:10.1016/S0002-9378(97)70187-X.
36
37
- 38
39 27. Finster M, Wood M. The Apgar score has survived the test of time.
40
41 *Anesthesiology.* 2005;102(4):855-857. doi:10.1097/00000542-200504000-00022.
42
43
- 44 28. Ehrenstein V, Pedersen L, Grijota M, Nielsen GL, Rothman KJ, Sørensen H.
45
46 Association of Apgar score at five minutes with long-term neurologic disability
47
48 and cognitive function in a prevalence study of Danish conscripts. *BMC*
49
50 *Pregnancy Childbirth.* 2009;9. doi:10.1186/1471-2393-9-14.
51
52
- 53 29. Krause Neto W, Gama EF. Exercise Effect on Placental Components: Systematic
54
55 Review and Meta-Analysis. *Rev Bras Med do Esporte.* 2015;21(6):485-489.
56
57
58
59
60

- 1
2
3 doi:10.1590/1517-869220152106142913.
4
5
6 30. Erkkola RU, Pirhonen JP, Kivijärvi AK. Flow velocity waveforms in uterine and
7
8 umbilical arteries during submaximal bicycle exercise in normal pregnancy.
9
10 *Obstet Gynecol.* 1992;79(4):611-615.
11
12
13 31. Takito MY, D'Aquino Benício MH, de Cassya Lopes Neri L. Physical activity by
14
15 pregnant women and outcomes for newborns: A systematic review. *Rev Saude*
16
17 *Publica.* 2009;43(6):1-10. doi:10.1590/S0034-89102009005000074.
18
19
20 32. Nielsen EN, Andersen PK, Hegaard HK, Juhl M. Mode of Delivery according to
21
22 Leisure Time Physical Activity before and during Pregnancy: A Multicenter
23
24 Cohort Study of Low-Risk Women. *J Pregnancy.* 2017;2017.
25
26 doi:10.1155/2017/6209605.
27
28
29 33. Jackson MR, Gott P, Lye SJ, Ritchie JW, Clapp JF. The effects of maternal
30
31 aerobic exercise on human placental development: placental volumetric
32
33 composition and surface areas. *Placenta.* 1995;16(2):179-191. doi:10.1016/0143-
34
35 4004(95)90007-1.
36
37
38
39 34. Márquez-Calderón S, Ruiz-Ramos M, Juárez S, López JL. Caesarean delivery in
40
41 Andalusia, Spain. Relationship with social, clinical and health services factors
42
43 (2007-2009). *Rev Esp Salud Publica.* 2011;85(2):205-215. doi:10.1590/S1135-
44
45 57272011000200008.
46
47
48 35. Organización Mundial de la Salud. *Declaración de La OMS Sobre Tasa de*
49
50 *Cesárea.*; 2015. doi:10.1016/j.rhm.2015.07.007.
51
52
53 36. Kodakkattil S, Annaiah TK. Re: Perinatal and maternal morbidity and mortality
54
55 among term singletons following midcavity operative vaginal delivery versus
56
57
58
59
60

- 1
2
3 caesarean delivery. *BJOG: An International Journal of Obstetrics and*
4
5 *Gynaecology*. 2017.
6
7
8 37. Hobbs AJ, Mannion CA, McDonald SW, Brockway M, Tough SC. The impact of
9
10 caesarean section on breastfeeding initiation, duration and difficulties in the first
11
12 four months postpartum. *BMC Pregnancy Childbirth*. 2016;16(1).
13
14 doi:10.1186/s12884-016-0876-1.
15
16
17 38. Bermúdez-Tamayo C, Johri M, Chaillet N. Budget impact of a program for safely
18
19 reducing caesarean sections in Canada. *Midwifery*. 2018;60:20-26.
20
21 doi:10.1016/j.midw.2018.01.022.
22
23
24 39. Bisson M, Tremblay F, St-Onge O, Robitaille J, Pronovost E, Simonyan D, Marc
25
26 I. Influence of maternal physical activity on infant's body composition. *Pediatr*
27
28 *Obes*. 2017;12:38-46. doi:10.1111/ijpo.12174.
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 1. Sociodemographic and clinical characteristic of the study sample (n=94).

Maternal outcomes	Mean (SD)
Age, years	32.9 (4.6)
Body mass index at 16 th gestational week, Kg/m ²	24.9 (4.1)
Living with a partner, n (%)	92 (97.9)
Educational status, n (%)	
<i>Primary or high-school</i>	26 (27.7)
<i>Professional training</i>	17 (18)
<i>University studies</i>	51 (54.3)
Working status, n (%)	
<i>Homework/unemployed</i>	26 (27.6)
<i>Partial-time employed/student</i>	24 (25.6)
<i>Full-time employed</i>	44 (46.8)
Type of delivery, n (%)	
<i>Spontaneous</i>	57 (60.6)
<i>Instrumental vacuum/forceps</i>	14 (14.9)
<i>Caesarean</i>	23 (24.5)
Parity, n (%)	
<i>Primiparous</i>	58 (61.7)
<i>Multiparous</i>	36 (38.3)
Sedentary time and PA, min/week	
<i>Sedentary time</i>	3598 (682.4)
<i>Light PA</i>	2733 (631.2)
<i>Moderate PA</i>	255 (148.4)
<i>Vigorous PA</i>	8 (21.5)
<i>Moderate-to-vigorous PA*</i>	95 (115.2)
<i>Total PA</i>	2997 (653.2)
<i>Steps per day, mean (SD)</i>	7745 (2559.6)
<i>Meeting PA guidelines, n (%)</i>	25 (26.6)
Smoker during pregnancy, n (%)	8 (8.5)
Neonatal outcomes	
<i>Sex (female, n (%))</i>	47 (50)
<i>Gestational age at birth, wk</i>	39.7 (1.2)
<i>Birth weight, grams</i>	3310 (468.3)
<i>Apgar Test 1 minute</i>	8.7 (0.9)
<i>Apgar Test 5 minutes</i>	9.6 (0.7)
Umbilical Cord blood Gas	
<i>Arterial pH</i>	7.2 (0.7)
<i>Arterial Partial Pressure CO₂, mmHg</i>	50.4 (9.9)

1		
2		
3	<i>Arterial Partial Pressure O₂, mmHg</i>	19.7 (8.8)
4	<i>Arterial O₂ saturation, %</i>	36.7 (22.4)
5	<i>Venous pH</i>	7.3 (0.6)
6		
7	<i>Venous Partial Pressure CO₂, mmHg</i>	39.2 (7.3)
8	<i>Venous Partial Pressure O₂, mmHg</i>	25.7 (7.2)
9		
10	<i>Venous O₂ saturation, %</i>	56.1 (17)

11 Values shown as mean (SD, standard deviation) unless otherwise indicated;
12 BMI, body mass index; CO₂, carbon dioxide; O₂, oxygen *accounted in
13 bouts of at least 10 minutes; min, minute; wk, week; PA, physical activity.
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

PROOF

Table 2. Partial correlations of sedentary time and physical activity levels with labour-related maternal and neonatal markers (n=94).

	Sedentary time	Light PA	Moderate PA	Vigorous VA	MVPA	Total PA	Steps per day
Labour-related outcomes							
Week of gestation (at birth) (n=88)	.120	-.140	-.125	.127	-.105	-.156	-.286**
Duration of first stage of labour (n=57)	.030	-.150	-.184	.043	-.179	-.188	-.274*
Duration of second stage of labour (n=60)	-.152	.106	.037	-.014	.040	.111	.133
Neonate-related outcomes							
Birth weight (n=87)	.018	-.052	-.144	-.088	-.156	-.084	-.208*
Apgar Test 1 minute (n=87)	.024	-.004	.032	-.365**	-.025	0.01	.029
Apgar Test 5 minutes (n=87)	-.040	.031	-.018	-.342**	-.070	.015	-.013
Cord blood arterial pH (n=67)	-.262*	.207	.016	.037	.024	.205	.058
Cord blood arterial partial pressure of CO ₂ (n=65)	.335**	-.198	-.071	-.015	-.076	-.207	-.069
Cord blood arterial partial pressure of O ₂ (n=61)	-.164	.191	.179	-.027	.177	.222	.228
Cord blood arterial oxygen saturation (n=59)	-.217	.209	.251*	.093	.266*	.263*	.318*
Cord blood venous pH (n=80)	-.267*	.251*	.099	-.012	.101	.264*	.166
Cord blood venous partial pressure of CO ₂ (n=79)	.299**	-.185	-.088	.102	-.078	-.195	-.071
Cord blood venous partial pressure of O ₂ (n=69)	-.044	.032	.079	-.219	.056	.044	.023

Model adjusted for age, parity, maternal body mass index, accelerometer wearing time and the exercise intervention; PA, physical activity; Carbon dioxide; O₂, Oxygen.

*P<0.05; **P<0.01;

Table 3. Differences in sedentary time and physical activity levels (min/week) of the pregnant women by delivery mode (vaginal or caesarean section).

	Vaginal (n=71)	Caesarean (n=23)	P	P*	Effect size <i>d</i>-Cohen
Sedentary time (min/day)	503.3 (11.5)	542.2 (20.1)	0.091	0.112	0.39 (-0.01, 0.79)
Light physical activity (min/wk)	2800.0 (72.6)	2617.1 (127.0)	0.088	0.223	0.29 (-0.10, 0.69)
Moderate physical activity (min/wk)	255.4 (16.4)	237.8 (28.8)	0.695	0.605	0.12 (-0.27, 0.52)
Vigorous physical activity (min/wk)	9.13 (2.5)	3.47 (4.3)	0.046	0.269	0.26 (-0.13, 0.66)
Moderate-to-vigorous physical activity ¥ (min/wk)	99.5 (12.0)	74.6 (21.0)	0.489	0.315	0.24 (-0.15, 0.64)
Total physical activity (min/wk)	3064 (75.8)	2858 (132.8)	0.073	0.189	0.31 (-0.08, 0.71)
Steps per day (number)	7865 (285.7)	7105 (500.2)	0.180	0.199	0.31 (-0.09, 0.71)

*Model adjusted for maternal age, parity, maternal body mass index, accelerometer wearing time and the exercise intervention; Values shown as mean (standard error); ¥, in bouts of at least 10 minutes.

SUPPLEMENTARY MATERIAL**Table S1.** Inclusion and exclusion criteria in the GESTAFIT project.

Inclusion criteria

- Pregnant women aged 25-40 years old with a normal pregnancy course.
- Answering “no” to all questions on the PARmed-X for pregnancy.
- Being able to walk without assistance.
- Being able to read and write properly.
- Informed consent: Being capable and willing to provide written consent.

*In addition, specific inclusion criteria for data analysis are: gestational age at delivery of 37-42 weeks with single foetus, spontaneous or instrumental vaginal delivery, and caesarean without maternofoetal pathology (or any other indication that does not involve maternofoetal risk, such as disproportion, failed induction, no foetal progression or non-cephalic presentation), newborn with appropriate weight, Apgar score >7 in the 1st and 5th minute of life, cord blood pH (normal >7.20), and normal monitoring results.

Exclusion criteria

- Acute or terminal illness.
 - Malnutrition.
 - Inability to conduct tests for assessing physical fitness or exercise during pregnancy.
-

-
- 1
 - 2
 - 3
 - 4
 - 5
 - 6 - Underweight.
 - 7
 - 8 - Pregnancy risk factors (such as hypertension, type 2 diabetes, etc.).
 - 9
 - 10 - Multiple pregnancy.
 - 11
 - 12 - Chromosopathy or foetal malformations.
 - 13
 - 14 - Uterine growth restriction.
 - 15
 - 16 - Foetal death.
 - 17
 - 18 - Upper or lower extremity fracture in the past 3 months.
 - 19
 - 20 - Presence of neuromuscular disease or drugs affecting neuromuscular function.
 - 21
 - 22 - Being registered in another exercise program.
 - 23
 - 24 - Doing more than 300 minutes of at least moderate physical activity per week.
 - 25
 - 26 - Unwillingness either to complete the study requirements or to be randomised into the
 - 27 control or intervention group.
 - 28
 - 29
 - 30
 - 31
 - 32
 - 33
 - 34
 - 35
 - 36
 - 37
 - 38
 - 39
 - 40
 - 41
 - 42
 - 43
 - 44
 - 45
 - 46
 - 47
-

Figure S1. Flowchart of the participants for the specific study aims.

