Title: Analysis of data collected from right and left limbs: accounting for dependence and improving statistical efficiency in musculoskeletal research

Authors: Sarah Stewart, Janet Pearson, Keith Rome, Nicola Dalbeth, Alain C. Vandal

PII: S0966-6362(17)30974-8
DOI: https://doi.org/10.1016/j.gaitpost.2017.10.018
Reference: GAIPOS 5847

To appear in: *Gait & Posture*

Received date: 9-8-2017
Revised date: 5-10-2017
Accepted date: 13-10-2017

Please cite this article as: Stewart Sarah, Pearson Janet, Rome Keith, Dalbeth Nicola, Vandal Alain C.Analysis of data collected from right and left limbs: accounting for dependence and improving statistical efficiency in musculoskeletal research.*Gait and Posture* https://doi.org/10.1016/j.gaitpost.2017.10.018

Analysis of data collected from right and left limbs: accounting for dependence and improving statistical efficiency in musculoskeletal research

AUTHORS

Sarah Stewart[a], corresponding author: +64 21 176 7690; sarah.stewart@aut.ac.nz

Janet Pearson[b], janet.pearson@aut.ac.nz

Keith Rome[a], krome@aut.ac.nz

Nicola Dalbeth[c], n.dalbeth@auckland.ac.nz

Alain C. Vandal[b,d], alain.vandal@aut.ac.nz

[a]Department of Podiatry, Health & Rehabilitation Research Institute, Auckland University of Technology, Private Bag 92006, Auckland 1142, New Zealand Zealand.

[b]Department of Biostatistics & Epidemiology, Faculty of Health and Environmental Sciences, Auckland University of Technology, Private Bag 92006, Auckland 1142, New Zealand.

[c]Faculty of Medical and Health Sciences, The University of Auckland, Private Bag 92019, Auckland 1142, New Zealand.

[d]Ko Awatea, Counties Manukau District Health Board, Private Bag 93311, Auckland 1640, New Zealand.

Highlights

- Current statistical methods inefficiently account for paired-limb measurements

- Multivariate mixed-effects models provide more precise estimates
- Multivariate mixed-effects models generate results of greater efficiency and power

ABSTRACT

Objectives. Statistical techniques currently used in musculoskeletal research often inefficiently account for paired-limb measurements or the relationship between measurements taken from multiple regions within limbs. This study compared three commonly used analysis methods with a mixed-models approach that appropriately accounted for the association between limbs, regions, and trials and that utilised all information available from repeated trials.

Method. Four analysis methods were applied to an existing data set containing plantar pressure data, which was collected for seven masked regions on right and left feet, over three trials, across three participant groups. Methods 1-3 averaged data over trials and analysed right foot data (Method 1), data from a randomly selected foot (Method 2), and averaged right and left foot data (Method 3). Method 4 used all available data in a mixed-effects regression that accounted for repeated measures taken for each foot, foot region and trial. Confidence interval widths for the mean differences between groups for each foot region were used as a criterion for comparison of statistical efficiency.

Results. Mean differences in pressure between groups were similar across methods for each foot region, while the confidence interval widths were consistently smaller for Method 4. Method 4 also revealed significant between-group differences that were not detected by Methods 1-3.

Conclusion. A mixed effects linear model approach generates improved efficiency and power by producing more precise estimates compared to alternative approaches that discard information in the process of accounting for paired-limb measurements. This approach is recommended in generating more clinically sound and statistically efficient research outputs.

KEYWORDS: Plantar pressure; Gait; Statistical analysis; Lower limb; Foot; Mixed effects models; Statistical efficiency

INTRODUCTION

Most rheumatic diseases, including rheumatoid arthritis, gout, osteoarthritis, psoriatic arthritis and spondyloarthropathy, present with a variety of musculoskeletal manifestations. Gout, osteoarthritis and psoriatic arthritis are often characterised by an asymmetrical pattern of distribution with regard to musculoskeletal symptoms, in that right and left limbs are not always affected equally. Clinical research in musculoskeletal rheumatology often involves the collection of data from right and left limbs from the same participant, resulting in limb-specific units of analysis, as opposed to person-specific units of analysis that occur when data are collected on single organ systems. However, person-specific and disease-specific factors, including age, gender, ethnicity, disease duration and the use of pharmacological therapy, result in a high level of within-subject dependence between limbs, meaning that data from right and left limbs are often highly correlated [1]. The same is true for multiple measurements taken from each limb, including from a range of joints or regions within limbs. This becomes problematic in the application of many commonly used statistical procedures, including linear models (such as the t-test and analysis of variance) that assume each data point is an independent observation [2].

It is not uncommon for researchers to pool data from right and left sides without accounting for the between-side correlation [3, 4]. This approach is often considered a valid method if the dependent variables of interest are limb-specific rather than person-specific. Pooling of right and left limb data also provides an appealing option as it apparently doubles the sample size while maintaining the same number of participants. However, pooling data results in artificial deflation of confidence intervals and significance levels [5, 6] that increases the probability of a type I error (rejecting the null hypothesis when it is true) compared to the nominal significance level α.

Several alternative methods have been used in musculoskeletal research to account for between-limb dependence, including undertaking a separate analysis of one or both limbs, whether this be the right and/or left [7-9], the most dominant side [10], the side with the most clinically evident symptoms of disease [11], or a randomly chosen side. However, such approaches result in a loss of valuable data and thus a reduction in statistical power and precision of estimates, and are overall inefficient methods of analysis. Furthermore, they may introduce a bias through the choice of which limb to use, particularly if a non-random selection approach is adopted.

Another commonly used method is to average data from right and left limbs. This becomes particularly problematic in rheumatic diseases that present with asymmetrical involvement, for example, osteoarthritis, gout and spondyloarthropathy, as averaging data may lessen the apparent magnitude of the disease and can lead to inaccurate inferences. Furthermore, without regarding the right and left sides as repeated within-subject measurements, efficiency and power are also lost. Similarly, averaging of repeated measurements is also common practice when measuring outcomes in quantitative research, whereby data is

obtained over multiple trials (generally three) for each limb and their average used in subsequent analyses. Averaging is primarily undertaken to reduce measurement error; however, this method also removes useful information when the number of averaged trials may differ. Inefficiencies also arise when variables measured from multiple joints or regions within each limb are analysed separately without appropriately accounting for between-region correlations [12].

The issue of between-limb dependence in statistical analysis has been identified in several research fields, including ophthalmology [13], podiatry [14, 15], orthopaedics [16] and rheumatology [17]. However, there is currently no consensus on the correct analytical approach of data collected from multiple trials from multiple limbs and/or regions within limbs. This article aims to compare three linear regression techniques, commonly used in current research under a generally incorrect assumption of independence between regions, with a mixed linear regression model that provides a more appropriate account for the association between limbs, regions, and trials, and that utilises all information available from repeated trials.

METHODS

Data set

For the purpose of illustrating the various analysis methods in the current article, peak plantar pressure data, a continuous variable measured in kilopascals (kPa), was taken from a larger data set [18]. The aim of the original study was to compare the plantar pressure distribution during barefoot walking in people with gout (n = 25) or people with asymptomatic

hyperuricaemia (n = 27) with that of healthy individuals with normal serum urate concentrations (n = 34). Plantar pressure data was collected for both right and left feet of each participant over three repeated walking trials. Peak plantar pressure was calculated for each of seven masked regions of the plantar foot representing the heel, midfoot, first metatarsal, second metatarsal, metatarsals three to four, the hallux and the lesser toes. For the full methodological protocol we direct readers to the original article [18].

Statistical analysis

Two comparisons were considered for all analytical approaches: gout vs. normouricaemic control and asymptomatic hyperuricaemic vs. normouricaemic control. Each analytical approach posited residual variances that differed at each of the seven masked regions of the plantar foot. Age and body mass index (BMI) were included in all analyses as covariates. To allow for systematic difference between left and right feet, a fixed effect for foot was added to Analysis Methods 2 and 4. The distribution of residuals for each linear model were examined to ensure demonstration of sufficient normality prior to undertaken the analyses. All hypothesis tests were carried out at a 5% level of significance against two-sided alternatives. All test statistics (least-squares means), their null distributions and their observed significance levels were reported. Data were analysed using SAS version 9.3. The data set was analysed using the following four approaches:

Analysis Method 1: The peak plantar pressure data obtained from the right foot only was used. The mean of the three repeated trials was calculated for each right foot and was analysed using linear regression models, in which peak plantar pressure was the dependent variable and the diagnostic group and covariates were included as fixed effects. Each of the

seven masked regions were analysed separately, resulting in the use of seven separate data sets.

Analysis Method 2: The peak plantar pressure data obtained from a randomly selected left or the right foot from each participant was used. The mean of the three repeated trials was calculated for each randomly selected foot and was analysed using the linear regression technique described above in Analysis Method 1.

Analysis Method 3: The mean peak plantar pressure values obtained over the three repeated walking trials were calculated for each participant's right and left foot. The right and left foot data was then averaged for each participant, and the resulting value was analysed using the linear regression technique described above in Analysis Methods 1 and 2.

Analysis Method 4: The single data set used by this method consisted of peak plantar pressure measurements for each trial, at all plantar masked regions, for both right and left feet. A mixed-effects linear regression model was used in which the fixed-effects of diagnostic group and covariates were nested within the plantar foot region variable. The diagnostic group and covariate effects were allowed to differ depending on the region. Repeated trial measurements taken from the right and left feet of each participant were accounted for using participant-specific random effects (fitting one parameter accounting for all covariances between measurements from different sides) and participant-nested random effects for foot side (fitting a distinct parameter accounting for all covariances between measurements from the same side and different trials). Additionally, the association between measures taken from the seven masked regions on the plantar foot, which form a natural vector of related variables, was taken into account by allowing a heterogeneous compound symmetry covariance structure on the model residuals that allowed for separate variances for each

region, as well as different covariances (but equal correlations, conditionally on the random effects) between each pair of regions. This model can be described as a mixed effects linear model [1], with repeated measures of peak plantar pressure at the seven masked regions on each side as the dependent variable.

It should be noted that it is possible to control for multiple testing [19] across the masked regions using any of the four Analytical Methods presented; to foster clarity and avoid controversy [20], we add no more on this topic. However only Analysis Method 4 allows a single general test of difference between diagnostic groups against a null of no difference in any of the regions. (The observed significance level of the region and diagnostic group interaction term is the p-value for this test.) One common practice is to carry out this general test, then delve into specific differences only if the alternative is accepted. Since we are proposing Analysis Method 4 as a candidate replacement for the other Analysis Methods, we emphasise estimation over testing in our presentation and eschew this practice.

An anonymous referee has recommended use of the Kenward-Roger method to estimate denominator degrees of freedom for the computation of test statistics and standard errors, in line with current best statistical practice. The reader, as a result, will notice some slight discrepancies between the results published herein and the results published in [18], although none of the conclusions are at variance.

SAS code for all Analysis Methods is provided in **Supplementary File 1**.

Method comparison

The criteria used to compare the four analysis methods consisted of the mean difference estimates and the width of the confidence intervals for the mean differences for each plantar

foot region. Confidence interval widths for the mean differences provide a convenient proxy for statistical efficiency. Statistical efficiency, hereafter simply efficiency, is formally defined as one over the asymptotic (large-sample) variance of an estimator [21]. As such, an increase in efficiency translates into increased precision of an estimate (i.e. decreased confidence interval width), and increased power and smaller observed significance levels in hypothesis tests when the alternative is true. Methods that increase statistical efficiency extract more information from any given set of data, and are therefore more statistically and scientifically appropriate.

RESULTS

Significant between-group differences were observed between gout and control participants, and asymptomatic hyperuricaemia and control participants, at only the midfoot from Analysis Methods 1 to 3 (**Tables 1**, **2**, and **3**, respectively). From Analysis Method 4, compared to controls, participants with gout had significantly reduced pressure at the heel and hallux and increased pressure at the midfoot, while participants with asymptomatic hyperuricemia had significantly increased pressure at the midfoot, first metatarsal and second metatarsal (**Table 4**). Estimated mean differences in peak pressure between diagnostic groups (**Figure 1A**) were similar across all analysis methods, while the confidence interval widths for the mean differences were consistently smaller for Analysis Method 4 (**Figure 1B**). The mean peak pressure estimates for each diagnostic group were also similar across analysis methods (**Figure 2A**), while confidence interval widths were again consistently lowest from Analysis Method 4 (**Figure 2B**).

DISCUSSION

This analysis compared three statistical approaches commonly used in the assessment of musculoskeletal outcomes in rheumatic diseases to analyse data collected from multiple limbs, regions and trials by discarding or averaging data, with a model that accounts for the association between limbs, regions and trials, and that utilises all data from repeated trials.

The results indicate that although all four methods produced similar mean peak pressure estimates, thereby demonstrating similar properties in regard to bias (in a statistical sense), the mixed effects linear model on non-averaged data consistently produced the narrowest confidence intervals for these parameters, when compared to the other three methods, and therefore demonstrated the greatest efficiency. This improved power and efficiency was achieved from utilising information present in the covariance between the areas of the feet, as well as the information present in each trial from both feet. Although the method that averaged data from right and left feet resulted in a loss of efficiency when compared to the mixed-effects model, it demonstrated narrower confidence intervals when compared to the methods that utilised only right foot data, or data from a randomly selected right or left foot. This resulted from the utilisation of information from both feet in the process of averaging data, since averaging reduces variance.

The loss of efficiency that occurs when independence between clusters (such as clusters of trials within region, regions within foot, or limbs within person) is assumed, can be large even for small to moderate correlations [22]. The mixed-effects model, which was designed along theoretical lines [22], enabled hitherto statistically nonsignificant between-group comparisons to be revealed as being actually statistically significant [18]. It is not uncommon

for studies of low statistical power and sample size to demonstrate non-statistically significant results that are clinically important [23, 24].

The mixed effects approach of Analysis Method 4 has a number of additional benefits. Firstly, utilisation of all data from both limbs means that all available information is retained. This is particularly important in rheumatic diseases such as osteoarthritis, gout and psoriatic arthritis, which have a tendency to monoarthropathy, meaning musculoskeletal pathology is commonly unilateral, especially in early disease stages. Secondly, Analysis Method 4 allows for analyses to be conducted using a single data set. This provides a more straightforward and time-friendly approach compared to running separate analyses for separate data sets as was undertaken in Analysis Methods 1 to 3. Thirdly, as it utilises data from both limbs without being labelled “double dipping” [15], it requires a smaller sample size than methods using single limb data, to achieve statistical power [25]. This has particular relevance to rheumatology research in which the vulnerability of potential participants often renders recruitment difficult. Fourthly, such models allow the introduction of individual limb- and region-specific covariates if desired, without difficulty, although we used no such covariates in the present work. Fifthly, another benefit in using a mixed effects linear model approach is that bias is reduced in fixed effect estimates in the presence of incomplete data, assuming that data are missing at random [1]. Finally, the mixed-effects approach has broad applicability and can extend both logistic and multinomial regression models in the case of binary and nominal dependent variables.

This article should be considered in light of a number of limitations. Firstly, several criteria provide between-model comparisons (i.e. Information Criteria) [26], but due to the different

processing of the repeated trials data (i.e. the trial averaging used in the first three models vs. the use of data from all trials for the mixed-effects model) and the different utilisation of left and right limb data, data sets differed and therefore, such criteria were not suitable to be used for comparison. That said, our purpose was not to look at prediction efficiency, which is optimised by some Information Criteria, but rather to look at the efficiency of estimation of means and mean differences between diagnostic groups, as provided by the confidence interval width measure. Secondly, the current article utilised SAS software to analyse the data, which may not be familiar to all researchers and may require researchers to seek additional statistical guidance. However, the syntax utilised in this article is provided as a Supplementary File to aid readers' understanding.

In conclusion, this article has shown how the adoption of a mixed linear regression model efficiently addresses the issue of between-limb dependence in musculoskeletal research through retaining individual side and trial data, and utilising the relationship between region measurements on the same foot. The improved efficiency and power generated from this model produces more precise estimates compared to alternative approaches that discard or average data, and which model region measurements independently. By adopting this method to analyse data collected from both right and left limbs, and from multiple regions within limbs, as well as across multiple trials, musculoskeletal rheumatology researchers would generate more clinically and statistically sound research outputs.

Conflicts of interest

Potential conflicts of interest may be created from consulting fees, speaker fees or grants received by N. Dalbeth (co-author) from the following companies: Takeda, Teijin, Menarini, Pfizer,

AstraZeneca, Ardea, Crealta, Cymabay, and Fonterra. The other authors declare no competing interests.

ACKNOWLEDGEMENTS: Arthritis New Zealand for funding the original work.

REFERENCES

[1] Brown, H, Prescott, R. *Applied Mixed Models in Medicine*. John Wiley & Sons, Incorporated: New York; 2014.

[2] Kenny DA, Judd CM. Consequences of violating the independence assumption in analysis of variance. *Psychol Bull* 1986;99:422-31.

[3] Kortekaas MC, Kwok W-Y, Reijnierse M, Kloppenburg M. Inflammatory ultrasound features shown independent associations with progression of structural damage after over 2 years of follow-up in patients with hand osteoarthritis. *Ann Rheum Dis* 2015;74:1720-4.

[4] Silva AC, Jones A, Silva PG, Natour J. Effectiveness of a night-time hand positioning splint in rheumatoid arthritis: a randomized controlled trial. *J Rehab Med* 2008;40:749-54.

[5] Rosner B. Multivariate methods in ophthalmology with application to other paired-data situations. *Biometrics* 1984;40:1025-15.

[6] Rosner B. Statistical methods in ophthalmology: an adjustment for the intraclass correlation between eyes. *Biometrics* 1982;38:105-14.

[7] Wang X, Blizzard L, Halliday A, Han W, Jin X, Cicuttini F, et al. Association between MRI-detected knee joint regional effusion-synovitis and structural changes in older adults: a cohort study. *Ann Rheum Dis* 2016;75:519-25.

[8] Rome K, Survepalli D, Sanders A, Lobo M, McQueen FM, McNair P, et al. Functional and biomechanical characteristics of foot disease in chronic gout: a case-control study. *Clin Biomech* 2011;26:90-4.

[9] Hennig T, Hæhre L, Hornburg VT, Mowinckel P, Norli ES, Kjeken I. Effect of home-based hand exercises in women with hand osteoarthritis: a randomised controlled trial. *Ann Rheum Dis* 2015;74:1501-8.

[10] Haugen IK, Slatkowsky Christensen B, Boyesen P, Sesseng S, van der Heijde D, Kvien TK. Increasing synovitis and bone marrow lesions are associated with incident joint tenderness in hand osteoarthritis. *Ann Rheum Dis* 2015;75:702-8.

[11] Glimm AM, Werner SG, Burmester GR, Backhaus M, Ohrndorf S. Analysis of distribution and severity of inflammation in patients with osteoarthitis compared to rheumatoid arthritis by ICG-enhanced fluorescence optical imaging and musculoskeletal ultrasound: a pilot study. *Ann Rheum Dis* 2015;75:566-70.

[12] Proschan MA, Waclawiw MA. Practical guidelines for multiplicity adjustment in clinical trials. *Control Clin Trials* 2000;21:527-39.

[13] Murdoch IE, Morris SS, Cousens SN. People and eyes: statistical approaches in ophthalmology. *Br J Ophthalmol* 1998;82:971-3.

[14] Menz HB. Two feet, or one person? Problems associated with statistical analysis of paired data in foot and ankle medicine. *Foot (Edin)* 2004;14:2-5.

[15] Menz HB. Analysis of paired data in physical therapy research: time to stop double-dipping? *J Orthop Sports Phys Ther* 2005;35:477-8.

[16] Orth P, Zurakowski D, Alini M, Cucchiarini M, Madry H. Reduction of sample size requirements by bilateral versus unilateral research designs in animal models for cartilage tissue engineering. *Tissue Eng Part C Methods* 2013;19:885-91.

[17] Sutton A, Muir K, Jones A. Two knees or one person: data analysis strategies for paired joints or organs. *Ann Rheum Dis* 1997;56:401-2.

[18] Stewart S, Dalbeth N, Vandal AC, Rome K. Spatiotemporal gait parameters and plantar pressure distribution during barefoot walking in people with gout and asymptomatic hyperuricemia: comparison with healthy individuals with normal serum urate concentrations *J Foot Ankle Res* 2016;9:15-23.

[19] Farcomeni A. A review of modern multiple hypothesis testing, with particular attention to the false discovery proportion. *Stat Methods Med Res* 2008;17:347–88.

[20] Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology* 1990;*1*:43-6.

[21] Casella G, Berger RL. *Statistical Inference*. 2nd ed. Pacific Grove: Duxbury; 2002.

[22] Mancl LA, Leroux BG. Efficiency of regression estimates for clustered data. *Biometrics* 1996;52:500-11.

[23] Freiman JA, Chalmers TC, Smith H, Jr., Kuebler RR. The importance of beta, the type II error and sample size in the design and interpretation of the randomized control trial. Survey of 71 "negative" trials. *N Engl J Med* 1978;299:690-4.

[24] Moher D, Dulberg CS, Wells GA. Statistical power, sample size, and their reporting in randomized controlled trials. *JAMA* 1994;272:122-4.

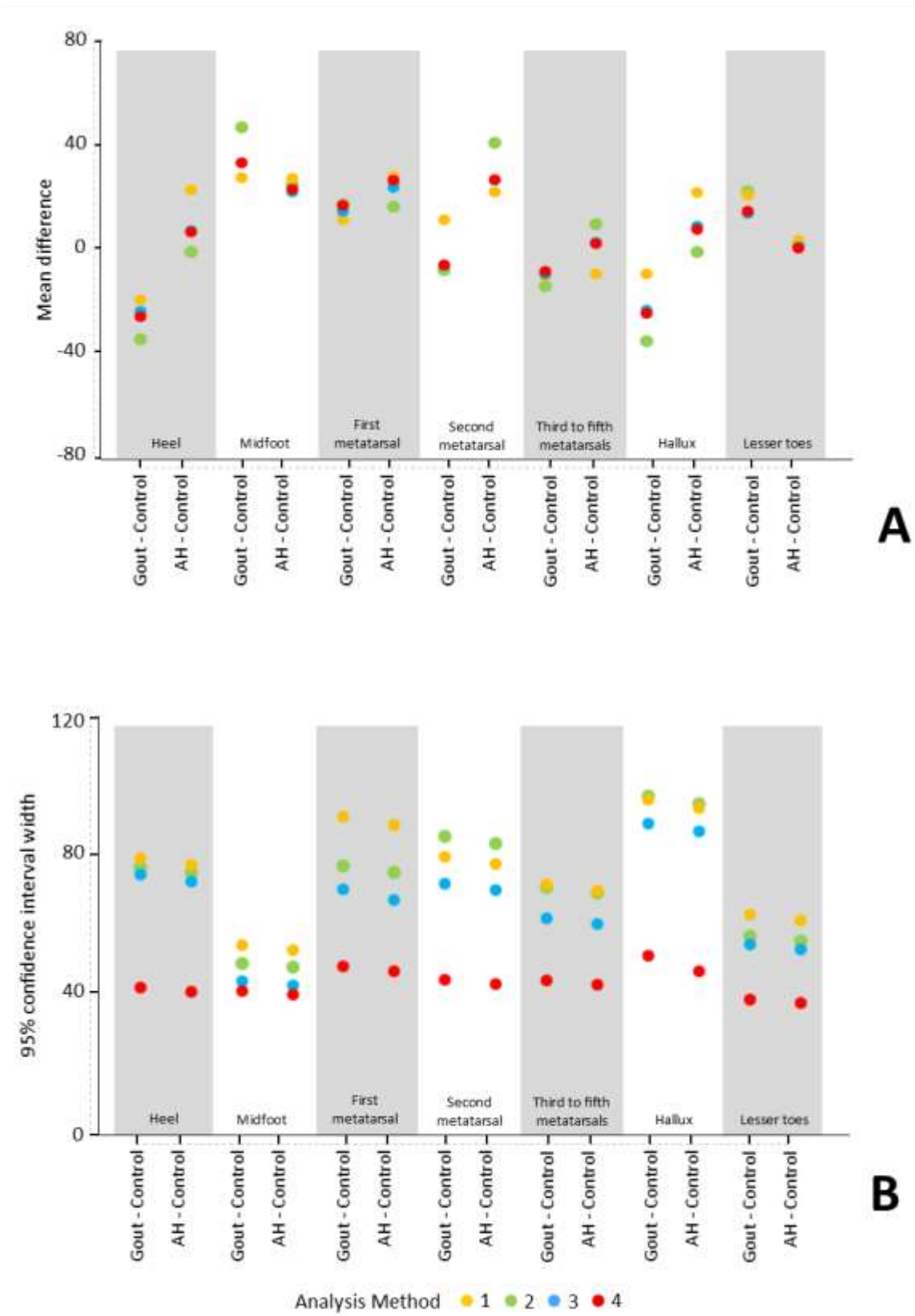
[25] Goodall EA, Moore J, Moore T. The estimation of approximate sample size requirements necessary for clinical and epidemiological studies in vision sciences. *Eye (Lond)* 2009;23:1589-97.

[26] Konishi S, Kitagawa G. *Information Criteria and Statistical Modeling.* Springer-Verlag: New York; 2008.

FIGURE LEGENDS

Figure 1. Mean difference in peak pressure (kPa) between diagnostic groups for sites (**A**) and 95% confidence interval widths for mean difference in peak pressure (kPa) between diagnostic groups for sites (**B**).

Figure 2. Mean peak pressure (kPa) estimates for each diagnostic group for sites (**A**) and 95% confidence interval widths for mean peak pressure (kPa) estimates for each diagnostic group for sites (**B**).



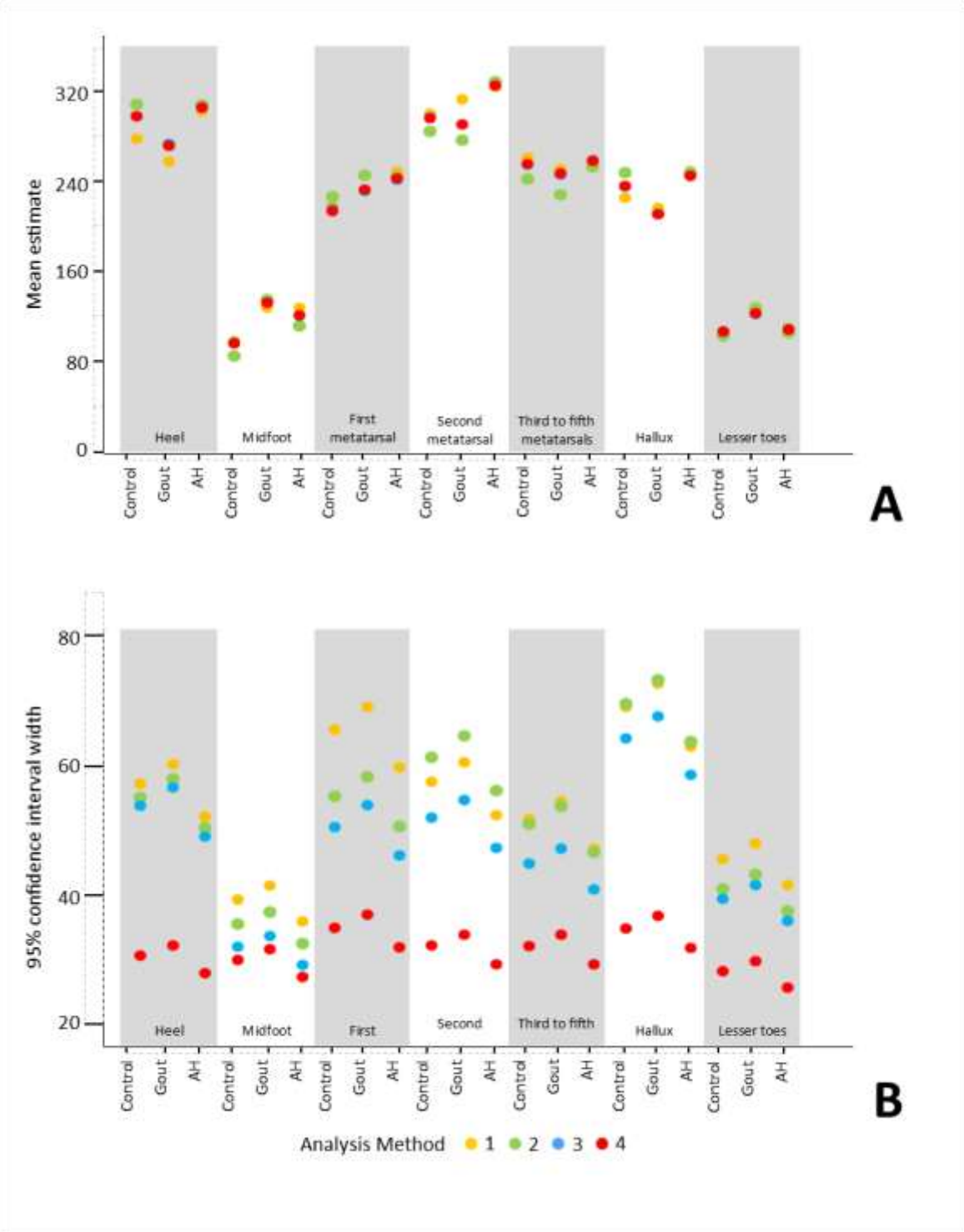


Table 1. Peak plantar pressure (kPa) using Analysis Method 1 (general linear regression analysing right foot data only)

Parameter		Least-squares mean	Diff.	95% CI Lower	95% CI Upper	*p*
Heel	Control	274.3				
	Gout	254.9	-19.5	-57.7	18.8	0.315
	Asymptomatic hyperuricemia	298.8	24.5	-12.8	61.8	0.196
Midfoot	Control	97.4				
	Gout	126.8	29.4	3.1	55.7	**0.029**
	Asymptomatic hyperuricemia	126.5	29.1	3.5	54.7	**0.027**
First metatarsal	Control	216.0				
	Gout	228.6	12.5	-31.4	56.5	0.571
	Asymptomatic hyperuricemia	245.9	29.9	-12.9	72.7	0.168
Second metatarsal	Control	296.5				
	Gout	309.1	12.6	-25.9	51.1	0.516
	Asymptomatic hyperuricemia	320.2	23.7	-13.8	61.2	0.212
Third to fifth metatarsals	Control	258.1				
	Gout	248.2	-9.9	-44.5	24.7	0.570
	Asymptomatic hyperuricemia	248.9	-9.2	-42.9	24.6	0.591
Hallux	Control	223.0				
	Gout	213.9	-9.1	-55.4	37.1	0.695
	Asymptomatic hyperuricemia	246.5	23.5	-21.5	68.6	0.302
Lesser toes	Control	104.5				
	Gout	127.0	22.4	-8.0	52.9	0.147
	Asymptomatic hyperuricemia	108.9	4.4	-25.3	34.1	0.769

Results are presented adjusted for age and BMI. Bolded *P* values indicate significant difference between groups at $P < 0.05$. Diff. = Difference in least-squares mean from control group; CI = Confidence Interval.

Table 2. Peak plantar pressure (kPa) using Analysis Method 2 (general linear regression analysing random left or right foot)

Parameter		Least-squares mean	Diff.	95% CI Lower	95% CI Upper	*p*
Heel	Control	304.5				
	Gout	269.2	-35.3	-72.3	1.7	0.061
	Asymptomatic hyperuricemia	304.1	-0.4	-36.6	35.7	0.982
Midfoot	Control	84.2				
	Gout	133.8	49.6	25.8	73.4	**<0.001**
	Asymptomatic hyperuricemia	110.8	26.6	3.4	49.9	**0.025**
First metatarsal	Control	223.8				
	Gout	242.5	18.7	-18.4	55.9	0.319
	Asymptomatic hyperuricemia	241.7	17.9	-18.4	54.2	0.329
Second metatarsal	Control	280.9				
	Gout	273.4	-7.5	-48.7	33.7	0.719
	Asymptomatic hyperuricemia	324.4	43.5	3.2	83.8	**0.035**
Third to fifth metatarsals	Control	239.3				
	Gout	225.4	-14.0	-48.2	20.3	0.419
	Asymptomatic hyperuricemia	250.1	11.0	-22.7	44.2	0.524
Hallux	Control	244.8				
	Gout	208.8	-36.0	-82.8	10.8	0.130
	Asymptomatic hyperuricemia	244.4	-0.4	-46.1	45.3	0.986
Lesser toes	Control	101.9				
	Gout	126.0	24.0	-3.5	51.6	0.086
	Asymptomatic hyperuricemia	104.5	2.54	-24.4	29.4	0.851

Results are presented adjusted for age and BMI. Bolded *P* values indicate significant difference between groups at $P < 0.05$. Diff. = Difference in least-squares mean from control group; CI = Confidence Interval.

Table 3. Peak plantar pressure (kPa) using Analysis Method 3 (general linear regression using data averaged from right and left feet)

Parameter		Least-squares mean	Diff.	95% CI Lower	95% CI Upper	*p*
Heel	Control	294.0				
	Gout	270.0	-24.0	-60.0	11.9	0.188
	Asymptomatic hyperuricemia	302.1	8.1	-27.0	43.2	0.647
Midfoot	Control	95.8				
	Gout	131.2	35.4	14.0	56.7	**0.002**
	Asymptomatic hyperuricemia	119.5	23.7	2.8	44.5	**0.026**
First metatarsal	Control	213.0				
	Gout	229.0	16.0	-18.0	49.9	0.353
	Asymptomatic hyperuricemia	238.5	25.5	-7.1	58.0	0.123
Second metatarsal	Control	293.0				
	Gout	287.3	-5.6	-40.4	29.1	0.748
	Asymptomatic hyperuricemia	321.4	28.4	-5.4	62.3	0.099
Third to Fifth metatarsals	Control	252.2				
	Gout	243.2	-9.0	-39.0	21.0	0.551
	Asymptomatic hyperuricemia	255.9	3.7	-25.5	32.9	0.802
Hallux	Control	232.4				
	Gout	208.7	-23.7	-66.7	19.3	0.276
	Asymptomatic hyperuricemia	242.5	10.1	-31.9	52.0	0.635
Lesser toes	Control	106.0				
	Gout	121.3	15.3	-11.0	41.7	0.251
	Asymptomatic hyperuricemia	107.7	1.7	-24.0	27.4	0.894

Results are presented adjusted for age and BMI. Bolded *P* values indicate significant difference between groups at $P < 0.05$. Diff. = Difference in least-squares mean from control group; CI = Confidence Interval.

Table 4. Peak plantar pressure (kPa) using Analysis Method 4 (mixed linear regression with random effects to account for paired foot data and related plantar foot sites)

Parameter		Least-squares mean	Diff.	95% CI Lower	95% CI Upper	*p*
Heel	Control	294.2				
	Gout	268.2	-26.1	-46.5	-5.6	**0.013**
	Asymptomatic hyperuricemia	302.0	7.7	-12.2	27.7	0.445
Midfoot	Control	95.4				
	Gout	130.8	35.4	15.4	55.5	**0.0006**
	Asymptomatic hyperuricemia	120.1	24.7	5.2	44.2	0.0134
First metatarsal	Control	211.5				
	Gout	229.7	18.2	-5.2	41.6	0.126
	Asymptomatic hyperuricemia	239.7	28.3	5.6	51.0	**0.015**
Second metatarsal	Control	292.6				
	Gout	287.1	-5.5	-27.0	16.0	0.614
	Asymptomatic hyperuricemia	321.4	28.8	7.8	49.7	**0.007**
Third to fifth metatarsals	Control	252.2				
	Gout	244.1	-8.2	-29.6	13.3	0.455
	Asymptomatic hyperuricemia	255.2	3.0	-18.0	23.9	0.780
Hallux	Control	233.2				
	Gout	208.4	-24.8	-48.2	1.5	**0.037**
	Asymptomatic hyperuricemia	241.9	8.7	-14.1	31.4	0.454
Lesser toes	Control	105.9				
	Gout	121.8	15.9	-2.9	34.8	0.097
	Asymptomatic hyperuricemia	107.2	1.4	-17.0	19.7	0.883

Results are presented adjusted for age and BMI. Bolded *P* values indicate significant difference between groups at $P < 0.05$. Diff. = Difference in least-squares mean from control group; CI = Confidence Interval.