



Handwriting and pre-frailty in the Lausanne cohort 65+ (Lc65+) study



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ABSTRACT

Background: Frailty is detected by weight loss, weakness, slow walking velocity, reduced physical activity or poor endurance/exhaustion. Handwriting has not been examined in the context of frailty, despite its functional importance.

Objective: Our goal was to examine quantitative handwriting measures in people meeting 0, 1, and 2 or more (2+) frailty criteria. We also examined if handwriting parameters were associated with gait performance, weakness, poor endurance/exhaustion and cognitive impairment.

Methods: From the population-based Lc65+, 72 subjects meeting 2+ frailty criteria with complete handwriting samples were identified. Gender-matched controls meeting 1 criterion or no criteria were identified. Cognitive impairment was defined by a Mini-Mental State Examination score of 25 or less or the lowest 20th percentile of Trail Making Test Part B. Handwriting was recorded using a writing tablet and measures of velocity, pauses, and pressure were extracted.

Results: Subjects with 2+ criteria were older, had more health problems and need for assistance but had higher education. No handwriting parameter differed between frailty groups (age and education adjusted). Writing velocity was not significantly slower among participants from the slowest 20th percentile of gait velocity but writing pressure was significantly lower among those from the lowest 20th percentile of grip strength. Poor endurance/exhaustion was not associated with handwriting measures. Low cognitive performance was related to longer pauses.

Conclusions: Handwriting parameters might be associated with specific aspects of the frailty phenotype, but not reliably with global definitions of frailty at its earliest stages among subjects able to perform handwriting tests.

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1. Introduction

The term frailty operationalizes the concept of diminished physiological reserve in older people, who are at increased risk of serious adverse outcomes such as cognitive decline, loss of functional ability, falls, hospitalization and death (Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013). Fried and colleagues introduced a model that included indices of weight loss, objective weakness,

slowed walking velocity, poor endurance/exhaustion, and diminished physical activity (Fried et al., 2001). Rockwood and colleagues considered an alternate model that summed impairments and illnesses, termed the frailty index (Rockwood, Song, MacKnight, et al., 2005), which predicts outcomes equally well (Woo, Leung, & Morley, 2012). Frailty and its components are common in western (and likely other) older populations and a major public health concern (Danon-Hersch, Rodondi, Spagnoli, & Santos-Eggimann, 2012; Santos-Eggimann, Cuénoud, Spagnoli, & Junod, 2009).

Like walking, handwriting is a continuous cognitive-motor task acquired during development that requires high skill and cerebral activation (Planton, Jucla, Roux, & Démonet, 2013). Overall

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handwriting velocity (Burger & McCluskey, 2011) and legibility (van Drempt, McCluskey, & Lannin, 2011) decrease with age. Change in writing velocity with age includes both increased “on-tablet time” (in contact with a writing tablet) and “air time” (time not writing with the writing implement off the writing surface), while completing a writing task (Rosenblum & Werner, 2006). Moreover, writing improves with practice (Dixon, Kurzman, & Friesen, 1993) and older individuals use visual cues to assist in handwriting (Slavin, Phillips, & Bradshaw, 1996). Thus, changes are not immutable. Importantly, handwriting is not specifically included in the definition of frailty and thus it might provide an “independent” index that might be linked to distinct aspects of frailty.

The Lc65+ study is a population-based longitudinal study designed to examine the impact of frailty on aging and to determine its precursors and correlates. A previous study from the cohort showed that pre-frail individuals accounted for 25% of participants, while frail individuals accounted for only 2.5% of those at baseline (Danon-Hersch et al., 2012). The current study focuses on subjects who completed two triennial follow-up evaluations, taking the advantage of the introduction of quantitative measures of handwriting at 6-year follow-up. Our primary goal was to determine which aspects of handwriting are associated with Fried’s frailty phenotype and to determine if handwriting was associated with specific aspects of frailty or cognitive impairment.

We hypothesized that individuals, meeting 1, or 2 or more criteria of the frailty phenotype in Lc65+ study would exhibit changes in handwriting parameters including velocity, pressure, and pauses. Specifically, we hypothesized that handwriting velocity would be related to gait velocity, that pressure would be related to grip strength, and that pauses would be related to loss of energy. Last we explored the relationship between cognitive dysfunction and handwriting parameters.

2. Methods

2.1. Subjects

Details of Lc65+ have been reported (Santos-Eggimann, Karmaniola, et al., 2008). In brief, the original cohort consisted of 1422 subjects aged 65–70 at the time of study entry in 2004 who were randomly selected from the community and participated in a baseline assessment. The ethics committee of the Faculty of Biology and Medicine of the University of Lausanne has approved the study protocol. The group included in the current analysis was selected from participants assessed during the second follow-up visit (age 72–77 years) who had quantitative handwriting measures recorded. The sample comprised *all* subjects meeting 2 or more frailty criterion (2+) with complete handwriting samples *and* randomly selected sex-matched subjects from the remaining Lausanne 65+ cohort either meeting 1 criterion or having 0 criteria for frailty (see Figure, supplementary materials). Given the restricted age-range of the cohort, age-matching was not performed a priori, but age was compared between groups, and adjusted for in secondary analyses. Basic socio-demographic and anthropomorphic measures included age, sex, education, height and weight (allowing calculation of body mass index, BMI). Self-reported health conditions, including depressive symptoms and functional limitations were recorded.

2.2. Frailty definition and measures

The frailty phenotype was defined as presented in a recent study (Danon-Hersch et al., 2012). Components of frailty are described individually and were derived from standardized assessments (Santos-Eggimann et al., 2008) by analogy with the

studies by Fried (Fried et al., 2001). In brief, weight loss was defined by a report of involuntary weight loss in the previous year; grip strength was measured and impaired grip strength was defined as sex and BMI-specific cut-off based on Cardiovascular Health Study (CHS) data (Fried et al., 2001; Mathiowetz et al., 1985); poor endurance/exhaustion was based on answering “much” to the question “did you have feelings of generalized weakness, weariness, lack of energy in the last four weeks?”; slowness was defined by walking time over 20 m based on CHS sex- and height-specific cut-offs (Fried et al., 2001); low activity was based on physical activity self-report of all three of the following: <20 min of sports per week, walking <90 min per week and avoidance of climbing stairs and carrying light loads in daily activities.

We also identified subjects characterized by: weakness, slow gait, or poor endurance/exhaustion by reference to the total cohort. For these analyses we used empirical cut-offs based on all Lc65+ assessments at second follow-up visit. The grip strength cut-off was based on the lowest sex and BMI specific 20th percentile on cut-offs from the overall sample at the time of taking the handwriting sample. Similarly, gait velocity cut-off was based on the slowest gender- and height-specific 20th percentile speed over 20 m.

2.3. Specific health conditions

Self-reported health questions included physician’s diagnosis or treatment in the last year of the following: coronary heart disease, other heart disease (congestive heart failure, valvular disease, cardiomyopathy), stroke, diabetes, hypertension, hypercholesterolemia, chronic respiratory disease, osteoporosis, arthritis, cancer, gastrointestinal disease, and depression (Danon-Hersch et al., 2012). We coded subject as having no health problems, one health problem, or two or more problems.

2.4. Cognitive and functional measures

The MMSE is a standard global cognitive measure (Folstein, Folstein, & McHugh, 1975). Subjects with a MMSE score of 25 or lower were considered impaired; this cut-off has very good sensitivity and high specificity for Alzheimer dementia when applied to francophone populations (Nasreddine, Phillips, Bédirian, et al., 2005). In addition, the Trail Making Test Part B is a standard test of executive function requiring motor speed and set-switching (Arbuthnott & Frank, 2000). It has been associated with motor function related to frailty in people living in the community (McGough, Kelly, Logsdon, et al., 2011; Soumaré, Tavernier, Alpérovitch, Tzourio, & Elbaz, 2009). Beside scoring 25 or less on the MMSE, subjects were also considered cognitively impaired if performing in the slowest 20th percentile of the overall sample at Trail Making Test Part B. Need for assistance in instrumental (IADL) and basic activities of daily living (BADL) were recorded via subject questionnaire and subjects were coded as having no need for assistance (0), needing help in IADLs (Clegg et al., 2013) or needing help in BADLs (Fried et al., 2001).

2.5. Handwriting task

Writing was recorded using a writing tablet (WACOM Intuos 4L) with an instrumented pen (model KP-130), which could quantify three-dimensional aspects of copying: writing in the current study was based on measures on the surface of the table (x - y plane) and pressure was based on unit-less measures of pressure on the tablet surface. Participants wrote on a piece of A4 (landscape) paper taped onto the writing tablet linked to a desktop computer running a custom java-script freeware program to allow data-gathering from the tablet. Participants were explained the

purpose of the test, i.e., to investigate relationships between health and variations in handwriting pressure and velocity. As described next, there were three sampling periods during which participants wrote two sentences each.

After being allowed to become familiar with the pen, a card with one of two French language sentences was presented in a fixed sequence to participants. The first sentence was “La table est dans la salle à manger”. The second sentence was “La baignoire est dans la salle de bain”. The pairs were presented systematically three times, once early in interview after cognitive assessment, once in the middle of the interview after questions on health-related behaviors and last toward the end of the session after financial questions. The identical portion of the sentences (“est dans la salle”) was extracted from the complete sentences for quantitative analysis. The first trial appeared significantly different from the five other trials because of an “unnatural” handwriting pattern, with subjects often taking up the entire width of the paper (landscape-oriented page). Thus the first trial was considered to be a practice run and was not further analyzed, except as indicated. Trials 2–6 were used for primary analysis. Available measures included: total time to write the sentence (s), on-tablet time (s), total velocity (cm/s), contact velocity (based on on-tablet time, cm/s) and contact pressure (unit-less, with a range of 0 indicating no pressure to 32,767), total time of pauses between words (three gaps, s), and pause time (total time to write the sentence minus on-tablet time, s). We examined contact velocity, contact pressure, and total time of pauses between words based on our specific hypotheses and for data reduction. In addition we examined overall velocity as a global indicator that includes writing time and pauses.

2.5.1. Handwriting data extraction setup

The extraction of the data was performed on a laptop computer using Excel 2010 in the Microsoft Windows XP operating system. In order to have a precise estimate of pauses irrespective of handwriting style, the time between words in the common sentence fragments was specifically segmented. Overall mean values of the writing parameters were used for the analyses.

2.6. Statistical analysis

Demographic and baseline categorical variables were compared in bivariate analyses with Chi-squared tests. Non-parametric Kruskal–Wallis tests were used to compare continuous variables, including writing parameters (velocity, pressure, pause times) in subjects with 0, 1 or 2+ criteria. Given imbalances between groups, multivariate linear models adjusted for age and education were calculated using each handwriting measure as dependent measure and the frailty phenotype as the main predictor. Since frailty phenotype groups were matched for sex, group comparison was not adjusted for sex.

In a second set of analyses, we grouped subjects according to the presence or absence of slow gait, low grip strength, poor endurance/exhaustion and compared writing velocity, pressure, and pause time, respectively. We examined the relationship

between cognitive impairment and each of the handwriting parameters. Adjustments were made for age, gender and education in linear regression models developed for the analyses of subjects with impaired gait, grip strength, endurance/exhaustion symptoms and cognition.

Variability based on percent coefficient of variation in instantaneous writing velocity and pause times were compared across groups. Additionally we examined the relationship between the percent coefficient of variation in writing velocity and slow gait or cognitive impairment.

We performed statistical tests with *p* values threshold set at 0.05. All analyses were performed using STATA (v 12.1).

3. Results

3.1. Study population

A total of 72 subjects, 21 men and 51 women met 2+ frailty criteria and provided a complete set of writing samples (6 sentences). There were 58 subjects meeting 2 frailty criteria, 9 meeting 3 criteria, and 5 meeting 4 criteria. The same number of subjects was randomly selected by group matching on sex among the 596 subjects meeting 0 criteria and 180 subjects meeting 1 frailty criterion with complete writing data. Groups were comparable in terms of most measures, though the frailest group was slightly older and more educated (Table 1, supplementary materials). As expected, the groups fulfilling 1, and 2+ criteria were more likely to have medical conditions and to require assistance in ADLs. Among 84 subjects who came to the follow-up visit and did not complete the writing tasks, 14 (17%) met no criteria, 22 (26%) met 1 criterion, and 36 (43%) met 2+ criteria for frailty. Twelve (14%) could not be classified. Among those who provided incomplete samples (less than 6 sentences), 25 (41%) met no criteria, 19 (31%) met 1 criterion, and 16 (26%) met 2+ criteria. One (2%) could not be classified.

3.2. Overall comparisons

3.2.1. Frailty groups

Velocity (either overall or on-tablet), pressure and pause time did not differ significantly across groups. Though not statistically significant, frailer subjects showed consistently slightly higher velocity and lower pressures, while pauses were longest in those meeting 1 criterion for frailty (see Table 2, supplementary materials). All three groups slowed slightly yet showed decreasing pressure across trials (see Table 2 that shows trial 1 and the mean of trials 2–6). The change (difference) in handwriting parameters between trials 2 and 6 was not different between groups (data not shown). Intra-individual variability in on-tablet velocity and total time of pauses between words did not differ between groups (data not shown). In the sex-matched groups, after adjusting for age and education, group membership did not predict any of the writing parameters (overall or on-tablet writing velocity, pressure, pauses, or coefficient of variation in writing on-tablet velocity, data not shown).

Table 1
Demographics and baseline data among frailty groups.

	0 criteria (n = 72)	1 criterion (n = 72)	2+ criteria (n = 72)	<i>p</i> value
Age at examination	74.8 (1.47)	74.7 (1.48)	75.4 (1.38)	0.006
Mean value (SD)				
Education (higher/lower)	2/70	9/63	10/61 (1 missing)	0.047
Health conditions (0/1/2+)	11/23/38	6/23/43	3/13/56	0.017
MMSE	27.8 (1.68)	27.1 (2.25)	27.4 (2.07)	0.266
Mean value (SD)				
ADL (no help/IADL help/BADL help)	66/6/0	63/9/0	51/14/7	0.001

Table 2

Handwriting characteristics across frailty groups, mean values (SD). In each row, results of trial 1 (not analyzed statistically) and means of trials 2–6 with corresponding *p* values are displayed.

	Non-frail (N=72)	1 criterion (N=72)	2+ criteria (N=72)	<i>p</i> value [*]
Overall velocity (cm/s)				
• Trial 1	2.49 (0.85)	2.54 (0.92)	2.63 (0.98)	
• Mean of trials 2–6	2.36 (0.79)	2.40 (0.94)	2.43 (0.98)	0.999
Contact velocity (cm/s)				
• Trial 1	3.63 (0.99)	3.71 (1.13)	3.81 (1.22)	
• Means of trials 2–6	3.37 (0.93)	3.44 (1.15)	3.47 (1.19)	0.960
Pressure (unitless)				
• Trial 1	13,519 (4531)	13,075 (3736)	12,971 (4259)	
• Means of trials 2–6	13,307 (4403)	12,680 (3480)	12,620 (4386)	0.485
Pauses between words (s)				
• Trial 1	1.28 (0.48)	1.40 (0.68)	1.22 (0.39)	
• Means of trials 2–6	1.15 (0.37)	1.23 (0.43)	1.20 (0.44)	0.574

^{*} Unadjusted.

Table 3

Specific frailty dimensions. Mean values (SD) from trials 2–6. M=males; F=females. Significant results in bold (unadjusted $p < 0.05$). + indicates abnormal.

	Gait+	Gait–	Weak+	Weak–	Energy+	Energy–	Cog+	Cog–
Frequency	22	41	30	33	8	55	18	45
Male (<i>n</i>)								
Frequency	46	107	50	103	23	130	49	104
Female (<i>n</i>)								
Overall velocity M (cm/s)	2.47 (0.93)	2.55 (1.10)	–	–	–	–	2.23 (0.76)	2.64 (1.11)
Overall velocity F (cm/s)	2.15 (0.68)	2.42 (0.90)	–	–	–	–	2.28 (0.64)	2.37 (0.92)
Contact velocity M (cm/s)	3.56 (1.22)	3.61 (1.29)	–	–	–	–	3.35 (0.99)	3.70 (1.34)
Contact velocity F (cm/s)	3.16 (0.86)	3.44 (1.07)	–	–	–	–	3.31 (0.80)	3.38 (1.10)
Pressure M	–	–	14,038 (3867)	15,483 (4680)	–	–	13,783 (4876)	15,200 (4094)
Pressure F	–	–	10,900 (3199)	12,647 (3862)	–	–	11,821 (4069)	12,196 (3588)
Pauses ^a M (s)	–	–	–	–	1.06 (0.48)	1.23 (0.49)	1.42 (0.45)	1.13 (0.48)
Pauses ^a F (s)	–	–	–	–	1.22 (0.37)	1.17 (0.38)	1.25 (0.38)	1.15 (0.38)

^a Total time of pauses between words.

3.2.2. Specific frailty dimensions and cognitive impairment

For characteristics reflecting defined dimensions of frailty and for cognition, specific hypotheses-driven analyses were performed. For both sexes, lower overall writing velocity was found in subjects characterized by slow gait velocity (not statistically significant); lower writing pressure was found in those with low grip strength (significant in females) and a longer pause time between words was associated with lower cognitive performance (significant in men) in bivariate analyses (Table 3, supplementary materials). In multivariable models adjusting for age, education and gender, gait was not significant for overall writing velocity ($p = 0.1$) or on-tablet writing velocity ($p = 0.2$). Weakness was a significant predictor of pressure ($p = 0.005$). Poor endurance/exhaustion was not associated with total time of pauses between words ($p = 0.9$). Cognitive impairment was not associated with overall writing velocity ($p = 0.4$), on-tablet writing velocity ($p = 0.7$) and pressure ($p = 0.2$) but it was significant for the total time of pauses between words ($p = 0.02$). Neither gait nor cognitive impairment was associated with the coefficient of variation of overall or on-tablet velocity over writing trials 2–6 (gait: $p = 0.4$ and $p = 0.5$, respectively; cognitive impairment: $p = 0.9$ and $p = 0.2$, respectively).

4. Discussion

Handwriting has not previously been examined in the context of frailty. We did not observe a predicted pattern of handwriting change across the frailty spectrum in our study. There were no statistically significant associations between writing parameters and the frailty phenotype; hence spatio-temporal characteristics of handwriting may be a relatively insensitive indicator of pre-frailty or early frailty in this young-old population aged 72–77 years.

The consistent, yet statistically insignificant, changes in writing velocity we observed were counterintuitive. Writing velocity *increased* with increasing frailty yet *decreased* across trials in all groups. Pressure was *lower* with increasing frailty. There was also a decrease in pressure across trials in all groups. In contrast, there was no consistent pattern of change in pauses.

A factor that may account for the counterintuitive changes in writing velocity might be that among the more frail, less educated subjects did not complete the writing protocol (selective attrition). Frailer subjects who participated in this writing protocol were *more educated*, suggesting that they were selected and might have had better (faster) writing skills to begin with. Alternatively, higher education might be protective with respect to writing performance, even in the face of impending frailty. Another possibility is that, among subjects who completed the writing task, those who were frail “rushed” to complete the writing task. The task required keeping in mind the sentence while copying it down, thus taxing working memory. Overall, however, handwriting did not appear sensitive to early frailty in our population. One study that examined the relationship between handwriting and environmental exposure in adults found that while timed grooved pegboard tasks were sensitive to environmental lead exposure, handwriting was not (Grashow, Spiro, Taylor, et al., 2013), highlighting the fact that motor tasks are distinct.

Frailty measures overlap incompletely with each other according to a recent study that showed that only a minority of frail individuals were impaired on the Short Physical Performance Battery (SPPB) (Subra et al., 2012). Here we show that this incomplete overlap extends to other independent motor measures, such as handwriting. A number of recent studies have shown that not all frailty scales are equivalent in construction (Theou, Brothers, Peña, Mitnitski, & Rockwood, 2014) and predictive

ability (Malmstrom, Miller, & Morley, 2014). When we examined the relationship between handwriting and specific aspects of frailty, we found that gait was not significantly associated with overall writing velocity while weakness (grip strength) was associated with decreased writing pressure. Both were, however, altered in the anticipated directions. Poor endurance/exhaustion was not associated with pauses as envisaged, highlighting the complexity and challenges in interpreting self-reported measures. While objective measures of energy/exhaustion/fatiguing may be obtainable (Schnelle et al., 2012) handwriting did not appear to decline reliably across our groups.

Cognitive dysfunction, as defined by impairment on MMSE or slowness on Trail Making Test, Part B, was not significantly associated with writing velocity and pressure. Nevertheless, writing velocity was *consistently slower and pressure consistently lower* in the presence of cognitive impairment, particularly in men, while pauses were significantly longer in multivariate models. That estimates of pause time between words were higher with poor cognitive performance, is consistent with results from a study on writing in dementia and mild cognitive impairment that quantified pauses (Werner, Rosenblum, Bar-On, Heinik, & Korczyn, 2006). Other studies that looked at specific movements (Yan, Rountree, Massman, Doody, & Li, 2008) or at drawing circles (Schröter et al., 2003) in cognitively impaired subjects also showed less smooth and less consistent movements in cognitively impaired individuals. A recent study showed that the frailty index was related to neurocognitive speed, again highlighting the heterogeneity among frailty measures, but reinforcing a possible relationship to cognitive function (Rolfson et al., 2013).

By analogy to gait measurement in people with mild cognitive impairment, it was hypothesized that variability in performance across writing trials could also provide a more sensitive indicator of impairment (Dodge, Mattek, Austin, Hayes, & Kaye, 2012). Our results did not support this hypothesis.

Our population was relatively young; consequently our results cannot be generalized to the oldest old who are at greatest risk of frailty. Consistent with their young age, the majority of frailest subjects in our study only met 2 or more criteria for frailty. We did not have a sufficient number of subjects meeting 3 or more; hence our subjects can be considered mostly pre-frail or early-frail. It is clear that many frail subjects did not participate in the writing protocol. One could consider examining subjects with incomplete writing samples, either by interpolating missing data or by examining the available trial (s). Failing to write a sentence, as part of performing the MMSE, was associated with lower education in one study (Neri, Ongaratto, & Yassuda, 2012). Thus, we do not know if frailer or more cognitively impaired subjects might exhibit changes in handwriting, though they demonstrated an inability to complete the writing task, which itself might be an indicator of more advanced frailty. Our study was cross-sectional and predictive abilities or changes in handwriting would be important to examine since predictive abilities are not the same as discriminative abilities. Other writing parameters, such as stroke velocity, letter size (height or width) or in-air trajectories merit further exploration, as these have been affected by diseases such as Parkinson's disease (Rosenblum, Samuel, Zlotnik, Erikh, & Schlesinger, 2013). Inconsistency of handwriting movements has been found in patients with Alzheimer disease and Huntington disease (Slavin, Phillips, Bradshaw, Hall, & Presnell, 1999). Another drawback is that our sample of frail individuals was relatively small and some of the trends observed might prove significant in a larger sample. Age is an important factor in handwriting, especially with regards to in-air time, but was controlled for in our analyses (Caligiuri, Kim, & Landy, 2014; Rosenbaum, Engel-Yeger, & Fogel, 2013; Walton, 1997). A last concern is that of interpretation of our results. Handwriting is a complex function that involves

widespread neural networks (Planton, Jucla, Roux, & Démonet, 2013) with cognitive, linguistic and fine motor function each contributing to global writing parameters.

Strengths of the study include the fact that the sample was systematically identified from a random population-based cohort. Ongoing follow-up will allow us to determine the predictive ability of quantitative handwriting measures and their potential changes in a pure or incident frail group. The quantitative measures allowed us to examine specific aspects of handwriting and to relate them to specific frailty measures. In fact, this analysis suggests that global writing velocity may be correlated with gait velocity, while writing pressure is correlated with grip strength. Cognitive function may be related to pauses while writing. In addition, trends suggested that compensatory mechanisms help cognitively impaired individuals maintain their writing function. Though not specifically examined, the absence of statistically significant differences is likely partly related to subject self-selection (i.e. the more educated among the frail performed writing tests) and to the fact that we did not examine specific aspects of cognitive function that might be related to writing.

In conclusion, handwriting parameters examined in this study might be associated specifically with aspects of the frailty phenotype, but not reliably with global definitions of frailty at its earliest stages among subjects able to perform handwriting tests. Additional quantitative aspects of handwriting, of frailer subjects and the predictive ability of handwriting measures require further study.

Conflict of interest

None of the authors have conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.archger.2015.01.006>.

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