Ultrasound Measurement of Median and Ulnar Nerve Cross-Sectional Area in Acromegaly

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Context: Acromegalic patients may complain of sensory disturbances in their hands.

Objective: Our objective was to examine median (MN) and ulnar nerves (UN) of acromegalic patients with ultrasound (US) and to determine whether nerve abnormalities correlate with clinical parameters and nerve conduction studies (NCS).

Patients: We prospectively examined the MN and UN in 34 nondiabetic, acromegalic patients (18 females and 16 males; age range 18–79 yr) and 34 sex-, age-, and body mass index-matched controls with 17-5 MHz US.

Intervention: The MN was examined at the carpal tunnel (MN-Ct) and at mid-forearm (MN-f) levels; the UN at the mid-forearm (UN-f) and distal arm (UN-a). A total of 272 nerve cross-sectional areas (CSA) were recorded from both patients and controls. In addition, 22 patients underwent NCS.

Results: Nerves of acromegalic patients (MN-Ct = 16.5 ± 4.4 mm^2; MN-f = 10.5 ± 2.4 mm^2; UN-f = 9.5 ± 3.0 mm^2; UN-a = 13.1 ± 3.7 mm^2) had significantly ($P < 0.0001$) greater CSA compared with controls (MN-Ct = 7.4 ± 1.7 mm^2; MN-f = 5.5 ± 1.4 mm^2; UN-f = 5.3 ± 1.4 mm^2; UN-a = 6.6 ± 1.7 mm^2). NCS displayed at least one abnormality in 59% of patients. Acromegalic patients, grouped according to disease activity (14 controlled, 8 partially controlled, 12 uncontrolled), had significantly ($P < 0.0001$) greater CSA compared with controls. Nerve CSA were significantly greater in uncontrolled patients compared to controlled, both at MN-Ct and at UN-f levels ($P < 0.01$). Abnormal NCS were observed in five of seven uncontrolled patients and four of nine controlled patients. IGF-I levels, but not GH levels, were correlated with CSA ($r = 0.34$), whereas disease duration correlated with both nerve CSA and NCS ($r = 0.33$ and $r = 0.31$).

Conclusion: US identified a significantly increased volume of MN and UN in acromegalic patients. Peripheral nerve enlargement in acromegaly seems to be an intrinsic feature of the disease related to clinical control, disease duration, and IGF-I levels. **(*J Clin Endocrinol Metab* 93: 905–909, 2008)**

In regard to nerve involvement in acromegaly, most of the available literature focuses on the median neuropathy at the carpal tunnel level (1, 2). On magnetic resonance imaging, an elevated intraneural T2-weighted signal of the median nerve (MN), possibly related to intranervous edema, was found in symptomatic patients (3). Other data state that carpal tunnel syndrome (CTS) in acromegaly should be attributed to narrowing of the carpal tunnel (4) or to edematous synovial tissues compressing the MN (5). In addition, only a few papers deal with involvement of nerves other than the MN, such as the ulnar nerve (UN), to explain sensory disturbances that typically affect acromegalic patients' hands (1, 2, 5).

The aim of the present study was to determine the main features of nerves in these patients observed on high-resolution ul-

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Abbreviations: BMI, Body mass index; CSA, cross-sectional area(s); CTS, carpal tunnel syndrome; MN, median nerve(s); MN-Ct, MN at carpal tunnel; MN-f, MN at mid-forearm; NCS, nerve conduction study (or studies); OGTT, oral glucose tolerance test; UN, ulnar nerve; UN-f, UN at mid-forearm; UN-a, UN at distal arm; US, ultrasound.

trasound (US) and to establish whether some correlation exists between clinical and electrophysiological parameters and morphological nerve abnormalities.

Patients and Methods

Patients

Between January 2006 and July 2006, we prospectively examined a series of 34 consecutive patients [18 females and 16 males; age range, 18–79 yr (54.9 ± 3.20); body mass index (BMI), 25.2 ± 0.90 kg/m^2; disease duration range, 1–15 yr (5.1 ± 0.85)] affected by acromegaly and a control group of healthy volunteers matched for sex, age, and BMI [18 females and 16 males; age range, 23–79 yr (41.9 ± 4.62); BMI, 25.1 ± 0.75 kg/m^2]. The diagnosis of acromegaly was based on established criteria (6). No patients had diabetes mellitus or hypothyroidism. The study protocol was approved by the local ethical committee, and written informed consent was obtained from all patients and controls. At the beginning of the study, six patients had a new diagnosis and did not receive any previous treatment, 19 previously underwent transsphenoidal neurosurgery (10 of 19 were also treated with somatostatin analogs), seven underwent primary medical therapy with somatostatin analogs, and the remaining patient underwent radiotherapy and octreotide therapy. Disease activity was evaluated by GH measurement during oral glucose tolerance test (OGTT) and the basal value of IGF-I (6–8). At the time of US examination, eight patients had symptoms related to the CTS. Seven other patients had a history of carpal tunnel release. Twelve patients complained of sensory disturbances (numbness and paresthesias) in the territory of distribution of the UN. Fourteen were free of symptoms in the areas supplied by the MN and UN. For statistical analysis, on the basis of disease control, patients were subdivided into "controlled" (n = 14) and "uncontrolled" (n = 12) groups, according to the evaluation of acromegaly activity based on the lack of GH suppression during OGTT (<1 μg/liter), coupled with elevated IGF-I levels (6), and a "partially controlled" group (n = 8) when a discordance among GH after OGTT and basal IGF-I values was recorded.

US studies

US examination of the MN and UN was performed with a digital scanner (IU 22; Philips, Eindhoven, The Netherlands) equipped with a broadband (frequency band, 17-5 MHz) linear array transducer. Interpretation of the US images was based on measurement of the nerve cross-sectional area (CSA). In each study, the MN was evaluated at the proximal carpal tunnel (MN-Ct) and at the middle third of the forearm (MN-f). Then, the UN was examined in the arm (UN-a) and the forearm (UN-f). The CSA of the UN was calculated at the mid-distal arm level and at 10 cm proximally to the wrist crease. A total of 272 CSA of acromegalic patients' nerves were compared with the controls. All US studies were performed by a radiologist experienced in musculoskeletal US (A.T.) to avoid interobserver variability. A second specifically trained blinded nonradiologist observer (F.B.) calculated the nerve CSA again. Interobserver agreement was good (k = 0.91).

Neurophysiological examination

In 22 of 34 patients, electrophysiological nerve conduction studies (NCS) of motor and sensory function of the MN and UN were performed bilaterally. Values of the distal motor and sensory latencies, motor and sensory nerve conduction velocities, and amplitude of evoked potentials were adjusted according to the patients' age, and the nerve was examined as described elsewhere (9). NCS severity was evaluated according to the existing classifications (10).

Laboratory assays

Serum GH levels were determined by means of an immunochemiluminometric assay, and IGF-I was measured by a RIA using immunochemicals and tracer provided by Biosource (Nivelles, Belgium) previously reported (11). IGF-I was measured in basal conditions, and it was reported as age-based SD scores, calculated on the basis of data obtained from over 4000 normal subjects of both sexes from 0 to 100 yr of age, grouped into decades of age.

Statistical analysis

Statistical analysis was performed using the Mann-Whitney *U* test for unpaired data to compare patients and controls, as well as patient groups. Values were expressed as mean ± SD. P values < 0.05 were considered statistically significant. To correlate nerve CSA with other parameters, the Pearson's test and linear regression analysis were used.

Results

Nerves of acromegalic patients had a significantly ($P < 0.0001$) greater CSA compared with controls at the four measurement sites (Fig. 1 and Table 1). At the carpal tunnel level, the MN CSA in acromegalic patients did not correlate with clinical symptoms, NCS, or previous surgery for CTS, even if enlarged. Moreover, NCS did not correlate with circulating levels of GH and IGF-I. Considering 10 mm^2 as a widely accepted threshold value for CTS (12), 31 of 34 (91%) patients exceeded this value, whereas only 14 of 34 (41%) referred typical clinical symptoms of CTS. In addition, seven of nine patients with negative NCS showed enlarged MN (CSA < 10 mm^2). In regard to possible links between CSA, GH, and IGF-I levels, a positive correlation was recorded between GH and IGF-I (r = 0.68; $P < 0.001$), and, although weak, between IGF-I and CSA at the different sampling sites (r = 0.34; $P < 0.01$). Instead, no correlation between CSA and GH levels existed (r = 0.03; $P < 0.01$). In terms of disease duration, a positive correlation was found between this parameter and either nerve CSA (r = 0.33; $P < 0.01$) or the severity of NCS (r = 0.31; $P < 0.01$) (Fig. 2). Controlled ($P < 0.0001$),

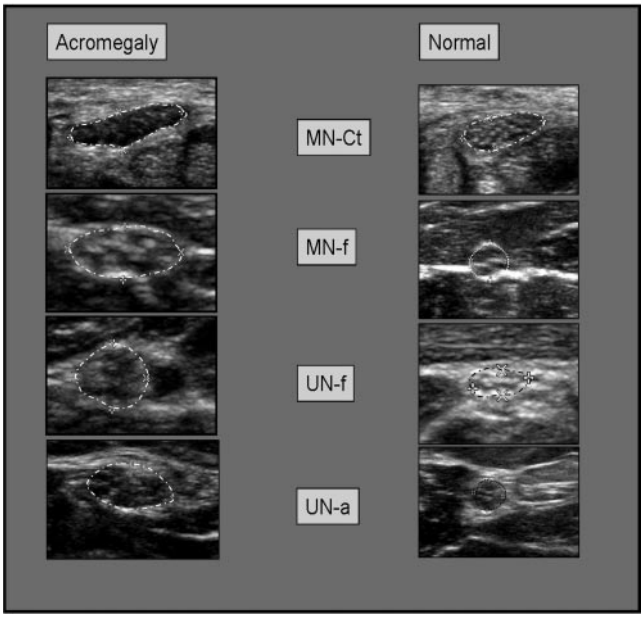

FIG. 1. Ultrasnographic comparison of nerves of acromegalic patients (*left*) and controls (*right*) at the four points of measurement. The nerve appears enlarged at the four points of sampling. Note the position of the calipers used to calculate the long and short axis of the nerve.

TABLE 1. Clinical and ultrasonographic data, CSAs of the acromegalic patients, grouped according to clinical activity of the disease, and controls

	Acromegalic patients (n = 34)			
	Controlled (n = 14)	Uncontrolled (n = 12)	Partially (n = 8)	Controls (n = 34)
Age (yr)	61.25 ± 2.74	48.00 ± 2.08	51.65 ± 5.08	41.9 ± 4.62
Sex (F/M)	8/5	8/5	3/5	18/16
IGF-I SD score	0.85 ± 0.18	5.86 ± 0.93	2.22 ± 0.25	
GH nadir (ng/ml)	0.37 ± 0.37	13.49 ± 4.97	0.85 ± 0.97	
MN-f	10.18 ± 2.53	10.84 ± 2.17	10.79 ± 2.94	5.55 ± 1.40
UN-f	10.17 ± 2.68	9.78 ± 2.41	9.44 ± 2.97	5.31 ± 1.43
UN-a	12.34 ± 2.77	14.95 ± 3.98*	12.39 ± 2.08**	6.66 ± 1.74
MN-Ct	15.46 ± 4.17	18.41 ± 4.14*	14.80 ± 4.01**	7.40 ± 1.70

Nerve CSA is expressed in square millimeters. Data are expressed in mean ± SD.

All groups *vs.* controls: $P < 0.0001$; *, $P < 0.01$ *vs.* controlled; **, $P < 0.02$ *vs.* uncontrolled.

uncontrolled ($P < 0.0001$), and partially controlled ($P < 0.0001$) patients had significantly enlarged nerves compared with the controls (Table 1).

Assessments within the acromegalic patients group

Comparison between controlled and uncontrolled patients revealed significantly greater CSA in uncontrolled patients for the MN-Ct and the UN-a ($P < 0.01$). Similarly, uncontrolled patients had significantly greater CSA than partially controlled patients at the same sites as above ($P < 0.02$). No difference between partially controlled and controlled patients was observed (results summarized in Table 1).

Neurophysiological studies

At electrophysiology, 13 of 22 (59%) reported at least one abnormal finding. No statistical correlation was observed between nerve CSA and electrophysiological data. NCS were abnormal in five of seven uncontrolled, four of nine controlled, and four of eight partially controlled patients.

Discussion

First reported in 1891, peripheral neuropathy is a rather common manifestation of acromegaly (13). In this disorder, the nerve involvement is multifaceted and may be recognized with difficulty, especially in patients with systemic complications (14). Usually patients complain of sensory disturbances in their hands and feet, including tingling, numbness, dysesthesias, and burning pain, and at disease presentation CTS occurs with a prevalence as high as 64% of cases (1, 3, 5, 15). Even if asymptomatic, most patients with acromegaly have subclinical functional abnormalities detected on NCS (4). From the pathophysiological point of view, there is no consensus in literature to explain the nerve involvement in acromegaly, whether it may be secondary to intrinsic factors, including histopathological changes and intraneural edema, or extrinsic problems related to the fact that nerves cross joint passing through narrow passageways, the osteofibrous tunnels, within which they may undergo compression (3–5).

We studied nerves in patients with acromegaly using high-resolution US to assess the possible value of imaging in this heterogeneous and clinically challenging group. US allowed an accurate and reliable depiction of both MN and UN based on established criteria (16). On short-axis planes, nerves exhibited a well-defined honeycombing appearance made of multiple rounded hypoechoic fascicles embedded in the hyperechoic epineurium (Fig. 1). Whatever the sampling site and the nerve examined, nerves of acromegalic patients showed a significantly larger CSA compared with corresponding nerves of the control group. The nerve enlargement was diffuse throughout the upper extremity, indicating a disease-related process that was basically unrelated to entrapment syndromes. In addition, the fascicular echotexture was always preserved, a figure that may be lost in focal neuropathies. Among other peripheral neuropathies, the Charcot-Marie-Tooth syndrome is the only disorder presenting with US changes somewhat resembling those observed in acromegalic nerves, including diffuse multifocal nerve enlargement and preserved nerve echotexture (17). Other neuropathies, such as compressive syndromes, leprosy, fibrolipomatous hamartoma, hereditary neuropathy with liability to pressure palsy, stretching injuries, and lymphoma, may cause nerve swelling, but they typically involve one nerve only, in a more localized form and with loss of the fascicular echotexture (18, 19). In regard to quantitative measurements, the CSA of the MN at the carpal tunnel level in acromegalic patients exceeded the threshold value established for CTS in 91% of cases (12). Of these patients, 41% did not show clear clinical symptoms suggesting CTS. In patients with recognized disease, sonologists should therefore be advised not to consider the CSA of the MN over 10 mm^2 as a sign of nerve compression at the carpal tunnel. Otherwise, an overestimation of CTS prevalence in acromegaly may occur with this technique. Based on our series, the characteristics of nerve enlargement in acromegaly seem to reflect a specific disease-related process rather than the result of a compressive neuropathy. This is related to the fact that nerves appeared uniformly swollen outside osteofibrous tunnels and far from the sites at which they may undergo compression. At least for the carpal tunnel, a recent work based on four acromegalic patients with symptoms of median neuropathy stated that the predominant abnormality of median

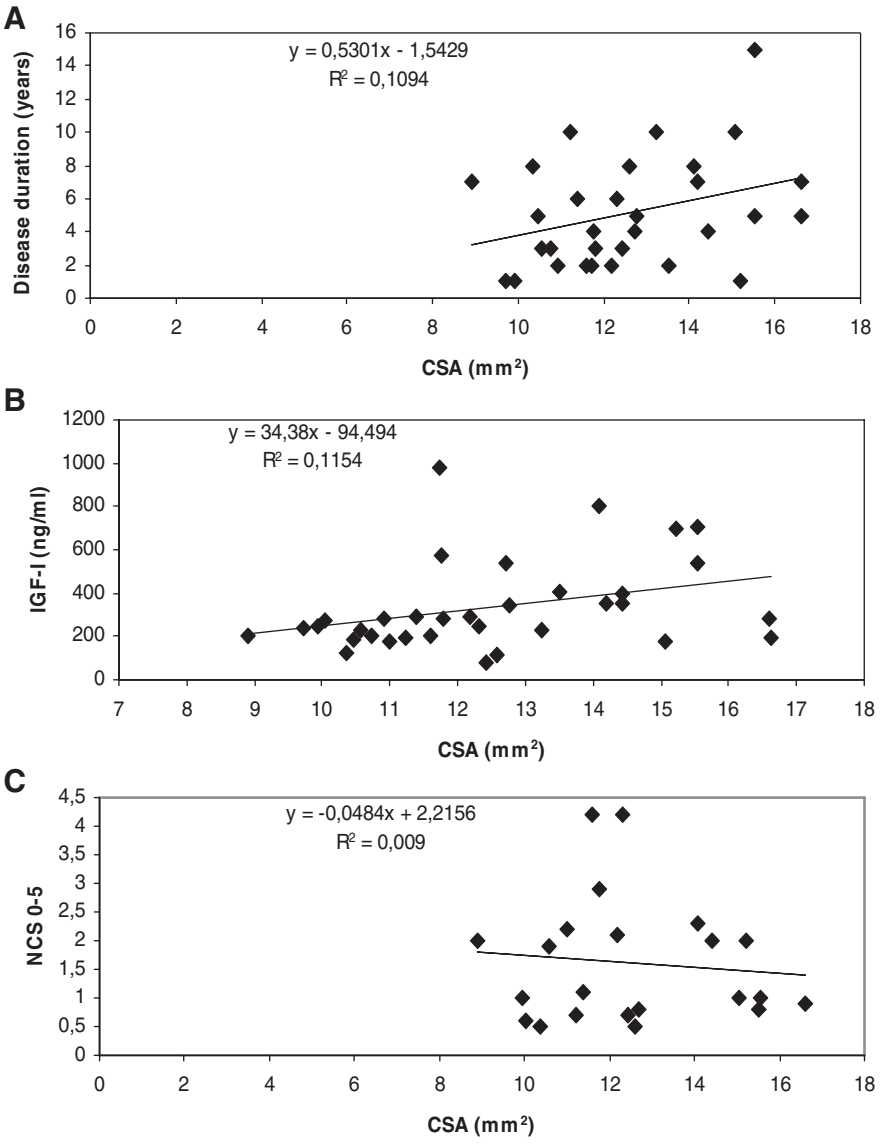

FIG. 2. Correlation between nerve CSA and disease duration (A), IGF-I (B), and NCS (C) ($P < 0.01$).

neuropathy in acromegaly is endoneural edema (3). It should be considered, however, that edema depicted as an increased signal intensity on T2-weighted magnetic resonance imaging sequences is also encountered in nonacromegalic patients with CTS (20). At least in part, intraneural edema should be causative of nerve enlargement, but it seems more likely to be a factor associated with axonal loss in a variety of pathological conditions, including entrapment syndromes, traumatic injuries, and infectious disease, rather than a specific indicator of acromegaly-related neuropathy (19). When we attempted to match the nerve CSA with electrophysiological parameters, we did not find any statistically significant correlation. Such a lack of correlation was, however, observed in other neuropathies, like compressive neuropathies (19) and the Charcot-Marie-Tooth syndrome (9). These data could reinforce the general opinion that the NCS parameters used to assess the nerve function are weakly linked to morphological changes. Correlation between clinical parameters and nerve CSA suggests that nerve size may be influenced by disease duration. In regard to hormone imbalance, our study reported a positive correlation between nerve CSA or NCS and IGF-I, but not with GH values. A significantly larger CSA and more severe NCS abnormalities were detected in uncontrolled patients at the carpal tunnel and at the UN-a when compared with controlled patients. These data suggest that nerves could be directly influenced by disease activity because morphological alterations are more obvious in patients with higher hormone levels.

In conclusion, our study suggests that nerves of acromegalic patients are significantly enlarged when compared with those of normal subjects. This finding seems to represent an intrinsic feature of the disease that is related to clinical control, disease duration, and IGF-I levels. Sonologists should become familiar with these abnormalities to avoid false positives of CTS when examining acromegalic patients. In addition, care should be taken if a diffuse enlargement of more than one nerve throughout the limbs and extremities without abnormalities in the fascicular echotexture is found. The possible occurrence of an acromegalic patient with unrecognized disease should be considered in the differential diagnosis list.

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References

1. **Colao A, Ferone D, Marzullo P, Lombardi G** 2004 Systemic complications of acromegaly: epidemiology, pathogenesis and management. Endocr Rev 25: 102–152
2. **Baum H, Ludecke DK, Hermann HD** 1986 Carpal tunnel syndrome and acromegaly. Acta Neurochir 83:54–55
3. **Jenkins PJ, Sohaib SA, Akker S, Phillips RR, Spillane K, Wass JA, Monson JP, Grossman AB, Besser GM, Reznek RH** 2000 The pathology of median neuropathy in acromegaly. Ann Intern Med 133:197–201

4. **Kaneyama S, Tanaka R, Hasegawa A, Tamura T, Kuroki M** 1993 Subclinical carpal tunnel syndrome in acromegaly. Neurol Med Chir (Tokyo) 33:547–551
5. **O'Duffy JD, Randall RV, MacCarty CS** 1973 Median neuropathy (carpal-tunnel syndrome) in acromegaly. A sign of endocrine overactivity. Ann Intern Med 78:379–383
6. **Giustina A, Barkan A, Casanueva FF, Cavagnini F, Frohman L, Ho K, Veldhuis J, Wass J, Von Werder K, Melmed S** 2000 Criteria for cure of acromegaly: a consensus statement. J Clin Endocrinol Metab 85:526–529
7. **Colao A, Lombardi G** 1998 Growth hormone and prolactin excess. Lancet 352:1455–1461
8. **Minuto F, Resmini E, Boschetti M, Arvigo M, Sormani MP, Giusti M, Ferone D, Barreca A** 2004 Assessment of disease activity in acromegaly by means of a single blood sample: comparison of the 120th minute postglucose value with spontaneous GH secretion and with the IGF system. Clin Endocrinol (Oxf) 61:138–144
9. 1993 Practice parameter for electrodiagnostic studies in carpal tunnel syndrome: summary statement. American Association of Electrodiagnostic Medicine, American Academy of Neurology, American Academy of Physical Medicine and Rehabilitation. Muscle Nerve [Erratum (1994) 17:262] 16:1390–1391
10. **Padua L, Lo Monaco M, Gregori B, Valente EM, Padua R, Tonali P** 1997 Neurophysiological classification and sensitivity in 500 carpal tunnel syndrome hands. Acta Neurol Scand 96:211–217
11. **Resmini E, Parodi A, Savarino V, Greco A, Rebora A, Minuto F, Ferone D** 2007 Evidence of prolonged orocecal transit time and small intestinal bacterial overgrowth in acromegalic patients. J Clin Endocrinol Metab 92: 2119–2124
12. **Lee D, van Holsbeeck MT, Janevski PK, Ganos DL, Ditmars DM, Darian VB** 1999 Diagnosis of carpal tunnel syndrome. Ultrasound versus electromyography. Radiol Clin North Am 37:859–872
13. **Marie P, Martinesco G** 1891 Sur l'anatomie pathologique de l'acromegalie. Arch Med Exp Anat Pathol 3:539–565
14. **Low PA, McLeod JG, Turtle JR, Donnelly P, Wright RG** 1974 Peripheral neuropathy in acromegaly. Brain 97:139–152
15. **Dinn JJ** 1985 Natural history of acromegalic peripheral neuropathy. Q J Med 57:833–842
16. **Silvestri E, Martinoli C, Derchi LE, Bertolotto M, Chiaramondia M, Rosenberg I** 1995 Echotexture of peripheral nerves: correlation between US and histologic findings and criteria to differentiate tendons. Radiology 197:291–296
17. **Martinoli C, Schenone A, Bianchi S, Mandich P, Caponetto C, Abbruzzese M, Derchi LE** 2002 Sonography of the median nerve in Charcot-Marie-Tooth Disease. AJR Am J Roentgenol 178:1553–1556
18. **Martinoli C, Derchi LE, Bertolotto M, Gandolfo N, Bianchi S, Fiallo P, Nunzi E** 2000 US and MR imaging of peripheral nerves in leprosy. Skeletal Radiol 29:142–150
19. **Martinoli C, Bianchi S, Gandolfo N, Valle M, Simonetti S, Derchi LE** 2000 US of nerve entrapments in osteofibrous tunnels of the upper and lower limbs. Radiographics 20:199–213
20. **Andreisek G, Crook DW, Burg D, Marincek B, Weishaupt D** 2006 Peripheral neuropathies of the median, radial, and ulnar nerves: MR imaging features. Radiographics 26:1267–1287