

eMethods

Study population. The Piemonte and Valle d'Aosta register for ALS (PARALS) is a prospective register enrolling all cases of ALS in the Piemonte and Valle d'Aosta regions of Italy (total population at the 2011 national census, 4,476,931; total area 28,692 sqkm). Epidemiological data regarding the 1995–2014 period have been published.¹ Data on the reference population have been obtained from the demographic websites of Piemonte (<http://www.demos.piemonte.it/>) and Valle d'Aosta regions (http://www.regione.vda.it/statistica/default_i.asp). During the study period the resident population remained quite stable, ranging from 4,401,266 in 2007 to 4,392,526 in 2016.

Sources of cases. The primary sources of cases are the two tertiary ALS centers (ALS Expert Centers), located in Torino and Novara, and the general Neurology Departments of the two regions. Every six months a search is also done for ALS diagnoses (ICD9 335.2 code) at the Piemonte and Valle d'Aosta Hospital Discharge Archives, which include information about all patients discharged by public and private hospitals of the two regions; for reimbursement reasons the Discharge Archives also collect data about the discharge of patients resident in the two regions who have been admitted to public and private hospitals located in other Italian regions. Annually, a search is also done for mortality data from Italian Statistical Bureau (ICD9 335.2 code). Clinical records of cases found through secondary sources are obtained both from the admitting hospitals and from the patients' general practitioner; relevant clinical information for each case are evaluated in order to verify if the patient meet the eligibility criteria; all living patients have been contacted by phone and visited by one of the neurologists involved in the study.

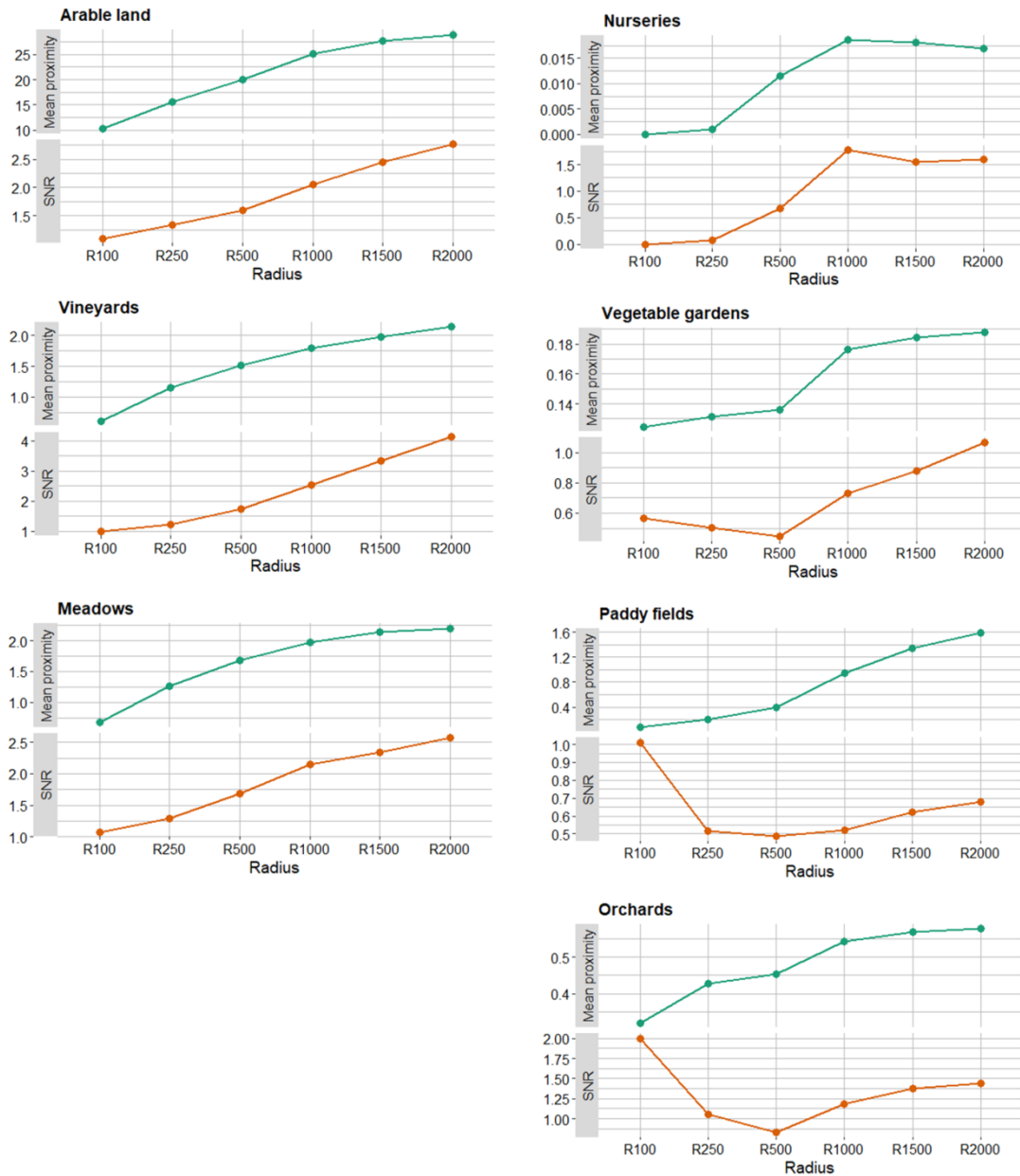
Diagnostic criteria. The diagnosis of ALS was based on the El Escorial Criteria revised (EEC-R).² Patients are included in the PARALS if they meet the diagnosis of definite, probable, probable laboratory-supported or possible ALS according to EEC-R at any stage of the disease.

Follow-up. Follow-up visits of each patient are performed at regular intervals (2 to 4 months). Local investigators use an ad hoc questionnaire to collect patients' demographic data, disease history, neurological and laboratory findings, including ALS functional rating scale, and treatments. At each visit, EEC-R diagnosis is verified and updated. Patients' date of death is obtained from the municipality offices where they resided.

Supplementary Table 1. Crops distribution in Piedmont. This table summarize the total area covered (m²) and the percentage of Piedmont area covered by each specific crop, the number of municipalities with a % of area covered by each crop >0 and the relative percentage on total numbers of municipalities.

| Crops | Area covered (m ²) | % area covered | Number of municipalities with % area covered >0 | % municipalities with at least % area covered >0 |
|-----------------|--------------------------------|----------------|---|--|
| Arable crops | 5,581,414,828 | 21.99% | 1168/1181 | 98.9 |
| Paddy fields | 1,035,886,075 | 4.08% | 117/1181 | 9.9 |
| Meadows | 555,873,325 | 2.19% | 410/1181 | 34.7 |
| Vineyards | 483,001,226 | 1.90% | 747/1181 | 63.3 |
| Orchards | 143,134,293 | 0.56% | 475/1181 | 40.2 |
| Vegetable crops | 43,156,569 | 0.17% | 360/1181 | 30.5 |
| Nurseries | 3,651,639 | 0.01% | 124/1181 | 10.5 |
| Olive groves | 480,091 | 0.002% | 91/1181 | 7.7 |
| Citrus groves | 3,219 | <0.001% | 4/1181 | 0.3 |

Supplementary Figure 1. This figure displays the Mean and the SNR of the proximity scores considering different radii for each cropland. A high SNR value indicates low variability between patients based on a specific cropland. Therefore, for each feature it is valuable to detect the shortest radius able to provide the greatest SNR value. Mean of all proximity scores at defined radius, green line; SNR, red line.



Supplementary Table 2. Age at onset and progression rate (Δ ALSFRS-R) at diagnosis according to the specific crop proximity score, calculated for different radii from residence at diagnosis (100, 250, 500, 1000, 1500, 2000 metres radii). Patients were classified in near and far patients for each specific crop for different radii. Near patients were defined by having a percentage >0 of area covered by the specific crop, while far patients were defined by having a percentage of area covered =0. Difference was calculated using Mann-Whitney U test and significant results ($p < 0.05$) are written in bold. Patients number=1098. IQR, interquartile range.

| Crops | N. of patients near/far | Near patients age at onset (years) | Far patients age at onset (years) | <i>p</i> | Near patients Δ ALSFRS-R (point loss per months) | Far patients Δ ALSFRS-R (point loss per months) | <i>p</i> |
|----------------------------|----------------------------|---------------------------------------|--------------------------------------|--------------|---|--|--------------|
| | | <i>Median (IQR)</i> | <i>Median (IQR)</i> | | <i>Median (IQR)</i> | <i>Median (IQR)</i> | |
| Arable crops 100 m radius | 421/677 | 68.0 (60.4-73.6) | 68.2 (60.2-74.7) | 0.363 | 0.662 (0.287-1.338) | 0.642 (0.3-1.292) | 0.494 |
| Arable crops 250 m radius | 682/416 | 67.8 (60.2-73.8) | 68.3 (60.4-75.6) | 0.183 | 0.626 (0.286-1.263) | 0.665 (0.332-1.377) | 0.114 |
| Arable crops 500 m radius | 826/272 | 67.6 (60.0-73.8) | 69.4 (61.2-75.9) | 0.011 | 0.645 (0.287-1.29) | 0.662 (0.33-1.345) | 0.227 |
| Arable crops 1000 m radius | 952/146 | 67.7 (59.9-73.9) | 69.4 (61.7-76.8) | 0.009 | 0.645 (0.29-1.292) | 0.688 (0.329-1.364) | 0.260 |
| Arable crops 1500 m radius | 1001/97 | 67.7 (60.1-74.2) | 69.6 (63.8-76.9) | 0.007 | 0.662 (0.296-1.323) | 0.599 (0.311-1.345) | 0.416 |
| Arable crops 2000 m radius | 1045/53 | 68.1 (60.2-74.3) | 69.2 (61.9-74.7) | 0.192 | 0.662 (0.3-1.323) | 0.605 (0.287-1.247) | 0.374 |
| Meadows 100 m radius | 44/1054 | 67.0 (64.0-74.1) | 68.2 (60.2-74.4) | 0.204 | 0.639 (0.295-1.093) | 0.649 (0.299-1.331) | 0.326 |
| Meadows 250 m radius | 96/1002 | 68.6 (63.1-74.4) | 68.1 (60.1-74.4) | 0.199 | 0.625 (0.326-1.033) | 0.657 (0.296-1.345) | 0.307 |
| Meadows 500 m radius | 148/950 | 68.6 (62.1-74.8) | 68.1 (60.1-74.3) | 0.113 | 0.675 (0.287-1.176) | 0.643 (0.3-1.343) | 0.394 |
| Meadows 1000 m radius | 203/895 | 68.0 (60.3-74.5) | 68.2 (60.2-74.3) | 0.347 | 0.597 (0.25-1.09) | 0.662 (0.31-1.362) | 0.062 |
| Meadows 1500 m radius | 226/872 | 67.8 (60.6-74.4) | 68.2 (60.2-74.3) | 0.361 | 0.583 (0.25-1.09) | 0.662 (0.312-1.36) | 0.041 |
| Meadows 2000 m radius | 243/855 | 67.4 (60.2-74.5) | 68.2 (60.3-74.3) | 0.450 | 0.582 (0.261-1.096) | 0.662 (0.31-1.362) | 0.041 |
| Nurseries 100 m radius | 1/1097 | 66.0 (66.0-66.0) | 68.2 (60.2-74.4) | 0.399 | 0.25 (0.25-0.25) | 0.652 (0.3-1.323) | 0.148 |
| Nurseries 250 m radius | 3/1095 | 66.9 (66.5-73.7) | 68.2 (60.2-74.4) | 0.265 | 0.501 (0.375-0.585) | 0.652 (0.299-1.328) | 0.232 |
| Nurseries 500 m radius | 12/1086 | 69.2 (65.6-72.0) | 68.1 (60.2-74.4) | 0.358 | 0.416 (0.25-0.604) | 0.662 (0.3-1.337) | 0.021 |
| Nurseries 1000 m radius | 35/1063 | 68.8 (62.9-74.6) | 68.1 (60.2-74.4) | 0.197 | 0.496 (0.25-0.831) | 0.662 (0.3-1.342) | 0.043 |

| | | | | | | | |
|-------------------------------|---------|---------------------|---------------------|-------|------------------------|------------------------|--------------|
| Nurseries 1500 m radius | 61/1037 | 68.4 (63.4-72.4) | 68.1 (60.2-74.4) | 0.314 | 0.501 (0.25-0.917) | 0.662 (0.304-1.353) | 0.023 |
| Nurseries 2000 m radius | 88/1010 | 69.6 (63.9-74.6) | 68.0 (60.1-74.3) | 0.130 | 0.533 (0.25-1.006) | 0.662 (0.304-1.353) | 0.069 |
| Orchards 100 m radius | 15/1083 | 63.5 (57.3-73.5) | 68.2 (60.3-74.4) | 0.201 | 0.597 (0.2-0.808) | 0.662 (0.302-1.334) | 0.055 |
| Orchards 250 m radius | 43/1055 | 69.6 (61.9-74.6) | 68.1 (60.2-74.4) | 0.269 | 0.605 (0.26-1.131) | 0.652 (0.302-1.338) | 0.207 |
| Orchards 500 m radius | 73/1025 | 69.6 (62.1-75.2) | 68.1 (60.2-74.3) | 0.170 | 0.718 (0.286-1.217) | 0.646 (0.3-1.323) | 0.436 |
| Orchards 1000 m radius | 132/966 | 68.6 (62.2-74.4) | 68.1 (60.2-74.4) | 0.285 | 0.584 (0.281-1.225) | 0.662 (0.308-1.333) | 0.177 |
| Orchards 1500 m radius | 192/906 | 68.4 (61.5-74.1) | 68.1 (60.2-74.4) | 0.387 | 0.59 (0.285-1.164) | 0.662 (0.308-1.345) | 0.124 |
| Orchards 2000 m radius | 245/853 | 68.3 (60.8-74.0) | 68.1 (60.2-74.4) | 0.494 | 0.584 (0.287-1.201) | 0.662 (0.304-1.345) | 0.158 |
| Paddy fields 100 m radius | 8/1090 | 70.5 (66.5-76.1) | 68.1 (60.2-74.3) | 0.127 | 0.815 (0.585-0.94) | 0.645 (0.299-1.331) | 0.394 |
| Paddy fields 250 m radius | 15/1083 | 70.3 (65.8-76.5) | 68.1 (60.2-74.3) | 0.131 | 0.88 (0.218-1.415) | 0.643 (0.3-1.323) | 0.425 |
| Paddy fields 500 m radius | 36/1062 | 70.5 (65.1-76.3) | 68.0 (60.2-74.3) | 0.078 | 0.723 (0.25-1.285) | 0.647 (0.304-1.331) | 0.397 |
| Paddy fields 1000 m radius | 59/1039 | 69.8 (63.8-75.5) | 68.0 (60.2-74.3) | 0.182 | 0.796 (0.262-1.285) | 0.643 (0.305-1.328) | 0.443 |
| Paddy fields 1500 m radius | 81/1017 | 69.8 (64.0-75.9) | 67.9 (60.1-74.3) | 0.062 | 0.615 (0.273-1.28) | 0.652 (0.307-1.336) | 0.374 |
| Paddy fields 2000 m radius | 87/1011 | 69.0 (63.8-74.9) | 68.0 (60.2-74.3) | 0.138 | 0.597 (0.273-1.206) | 0.662 (0.308-1.338) | 0.229 |
| Vegetable crops 100 m radius | 38/1060 | 66.1 (61.8-72.9) | 68.3 (60.2-74.4) | 0.427 | 0.584 (0.229-0.982) | 0.657 (0.303-1.334) | 0.146 |
| Vegetable crops 250 m radius | 76/1022 | 67.6 (62.1-74.4) | 68.2 (60.1-74.4) | 0.205 | 0.583 (0.245-0.999) | 0.662 (0.307-1.351) | 0.058 |
| Vegetable crops 500 m radius | 124/974 | 68.2 (62.0-74.6) | 68.2 (60.1-74.3) | 0.151 | 0.572 (0.233-1.004) | 0.662 (0.328-1.356) | 0.016 |
| Vegetable crops 1000 m radius | 182/916 | 67.8 (60.7-74.7) | 68.2 (60.1-74.3) | 0.229 | 0.597 (0.25-1.09) | 0.662 (0.324-1.347) | 0.046 |
| Vegetable crops 1500 m radius | 225/873 | 68.4 (60.7-74.6) | 68.1 (60.1-74.3) | 0.194 | 0.601 (0.251-1.101) | 0.662 (0.312-1.353) | 0.055 |
| Vegetable crops 2000 m radius | 260/838 | 68.4 (60.2-74.9) | 68.0 (60.2-74.2) | 0.188 | 0.601 (0.266-1.178) | 0.662 (0.312-1.351) | 0.098 |
| Vineyards 100 m radius | 38/1060 | 68.8 (61.8-72.4) | 68.1 (60.2-74.4) | 0.379 | 0.693 (0.299-1.363) | 0.647 (0.3-1.323) | 0.419 |

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|-------------------------|---------|---------------------|---------------------|-------|------------------------|------------------------|-------|
| Vineyards 250 m radius | 122/976 | 68.6 (62.4-73.4) | 68.0 (60.2-74.5) | 0.426 | 0.624 (0.284-1.213) | 0.657 (0.307-1.334) | 0.192 |
| Vineyards 500 m radius | 234/864 | 67.8 (60.2-74.3) | 68.2 (60.4-74.4) | 0.347 | 0.662 (0.274-1.323) | 0.645 (0.308-1.323) | 0.348 |
| Vineyards 1000 m radius | 363/735 | 67.4 (59.3-74.1) | 68.4 (60.8-74.7) | 0.084 | 0.643 (0.287-1.268) | 0.662 (0.305-1.342) | 0.285 |
| Vineyards 1500 m radius | 443/655 | 67.5 (59.3-74.3) | 68.4 (61.3-74.6) | 0.074 | 0.624 (0.275-1.232) | 0.667 (0.331-1.355) | 0.072 |
| Vineyards 2000 m radius | 489/609 | 67.4 (59.4-74.3) | 68.6 (61.3-74.6) | 0.075 | 0.629 (0.283-1.217) | 0.665 (0.331-1.367) | 0.069 |

Supplementary Table 3. Age at onset according to the specific crop proximity score, calculated for different radii (100, 250, 500, 1000, 1500, 2000 metres radii) using historical residence data, stratified for sex, site of onset (spinal vs. bulbar) and in wild-type patients. Patients were classified in near and far patients for each specific crop for different radii. Near patients were defined by having a percentage >0 of area covered by the specific crop, while far patients were defined by having a percentage of area covered =0. Difference was calculated using Mann-Whitney U test and significant results ($p < 0.05$) are written in bold. Data showed for significant intervals only. IQR, interquartile range.

| Crops | N. of patients near/far | Near patients age at onset (years) | Far patients age at onset (years) | Difference in median age at onset | |
|-------------------------------|----------------------------|---------------------------------------|---|--|--------------|
| | | Median (IQR) | Median (IQR) | Years | <i>p</i> |
| Female patients (N=511) | | | | | |
| Arable crops 100 m radius | 234/260 | 67.5 (60.2-73.8) | 69.4 (62.6-76.6) | 1.90 | 0.021 |
| Arable crops 250 m radius | 346/148 | 68.3 (60.8-74.5) | 69.5 (62.6-77.1) | 1.20 | 0.051 |
| Arable crops 500 m radius | 402/92 | 68.2 (61.0-74.7) | 69.9 (63.3-77.6) | 1.70 | 0.020 |
| Arable crops 1000 m radius | 445/49 | 68.4 (61.4-74.8) | 71.6 (64.5-78.2) | 3.20 | 0.011 |
| Vineyards 500 m radius | 135/359 | 66.7 (58.8-74.5) | 68.8 (62.5-75.8) | 2.10 | 0.043 |
| Vineyards 1000 m radius | 190/304 | 67.5 (59.3-74.2) | 69.1 (62.8-76.3) | 1.60 | 0.024 |
| Vineyards 1500 m radius | 226/268 | 67.7 (59.2-74.5) | 69.1 (63.7-76.2) | 1.40 | 0.027 |
| Male patients (N=566) | | | | | |
| Arable crops 100 m radius | 251/315 | 66.3 (59.2-72.1) | 69.2 (59.4-74.6) | 2.90 | 0.018 |
| Arable crops 250 m radius | 383/183 | 66.4 (58.5-72.7) | 69.6 (61.3-75.8) | 3.20 | 0.001 |
| Arable crops 500 m radius | 440/126 | 66.6 (58.8-72.9) | 70.3 (61.5-76.3) | 3.70 | 0.001 |
| Arable crops 1000 m radius | 501/65 | 67.1 (58.9-73.3) | 70.5 (61.1-76.4) | 3.40 | 0.019 |
| Arable crops 1500 m radius | 523/43 | 67.3 (59.0-73.4) | 70.5 (63.1-76.4) | 3.20 | 0.029 |
| Vineyards 1500 m radius | 247/319 | 66.3 (57.5-72.9) | 68.8 (61.0-73.8) | 2.50 | 0.014 |
| Vineyards 2000 m radius | 272/294 | 66.4 (57.6-73.3) | 68.8 (61.0-73.9) | 2.40 | 0.016 |
| Bulbar onset patients (N=362) | | | | | |
| Arable crops 100 m radius | 176/186 | 69.2 (63.6-74.8) | 71.0 (64.5-78.0) | 1.80 | 0.018 |
| Arable crops 250 m radius | 259/103 | 69.5 (63.6-76.2) | 72.9 (65.4-78.0) | 3.40 | 0.037 |
| Arable crops 500 m radius | 299/63 | 69.5 (63.6-76.3) | 73.2 (66.4-78.6) | 3.70 | 0.013 |
| Spinal onset patients (N=678) | | | | | |
| Arable crops 100 m radius | 304/374 | 65.8 (56.5-71.6) | 67.1 (58.9-74.0) | 1.30 | 0.012 |
| Arable crops 250 m radius | 457/221 | 65.8 (56.7-71.7) | 68.3 (60.7-74.7) | 2.50 | 0.000 |
| Arable crops 500 m radius | 530/148 | 65.9 (56.9-72.1) | 69.1 (61.0-75.7) | 3.20 | 0.000 |
| Arable crops 1000 m radius | 607/71 | 66.0 (57.2-72.5) | 69.6 (61.3-76.2) | 3.60 | 0.002 |
| Arable crops 1500 m radius | 634/44 | 66.1 (57.7-72.7) | 68.7 (61.8-76.4) | 2.60 | 0.032 |

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|-----------------------------------|---------|---------------------|---------------------|-------------|--------------|
| Vineyards 500 m radius | 166/512 | 65.0 (55.0-72.0) | 66.5 (58.9-73.0) | 1.50 | 0.025 |
| Vineyards 1000 m radius | 247/431 | 65.0 (54.6-72.4) | 66.8 (59.6-73.1) | 1.80 | 0.005 |
| Vineyards 1500 m radius | 304/374 | 65.0 (55.3-72.4) | 67.0 (60.1-73.6) | 2.00 | 0.004 |
| Vineyards 2000 m radius | 334/344 | 65.4 (55.4-72.4) | 67.0 (60.1-73.8) | 1.60 | 0.003 |
| Wild-type patients (N=787) | | | | | |
| Arable crops 250 m radius | 444/343 | 66.7 (59.6-72.8) | 68.6 (60.9-74.7) | 1.90 | 0.018 |
| Arable crops 500 m radius | 551/236 | 66.8 (59.7-73.0) | 69.3 (60.9-75.6) | 2.50 | 0.017 |
| Arable crops 1000 m radius | 635/152 | 67.1 (59.7-73.2) | 69.3 (61.4-76.3) | 2.20 | 0.019 |