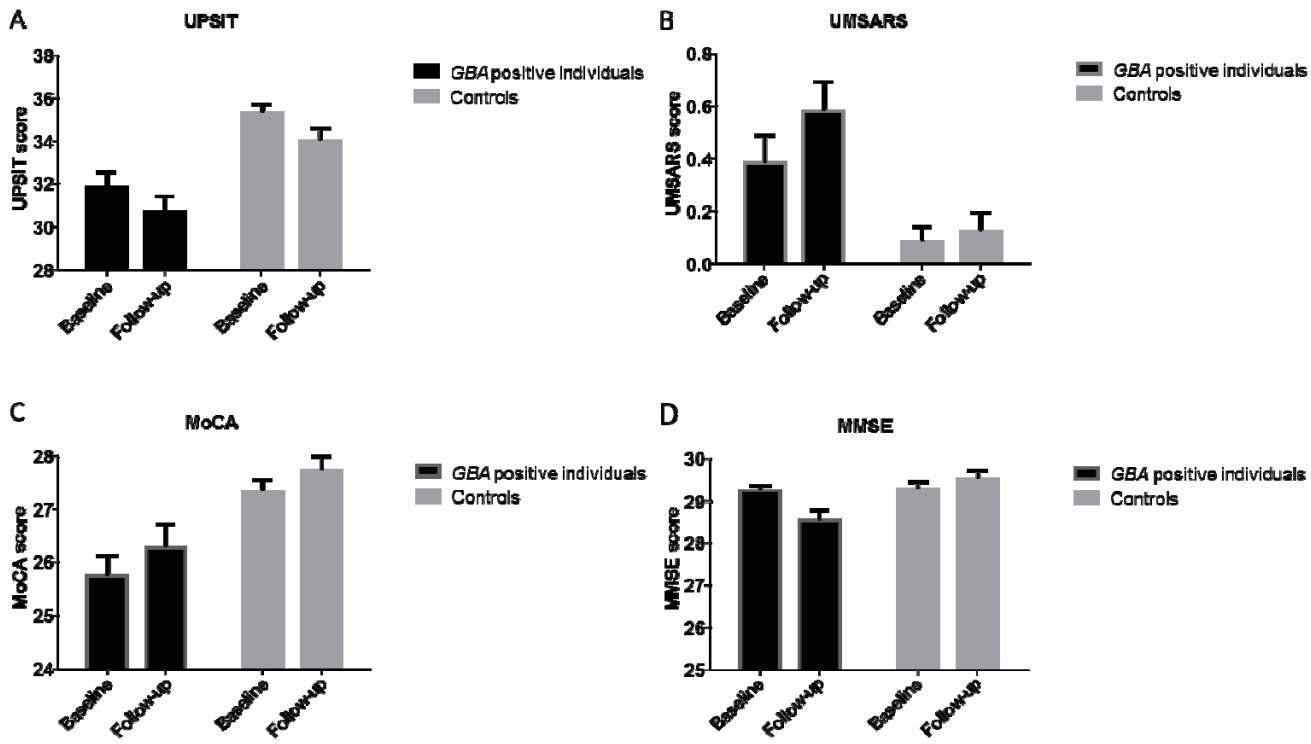
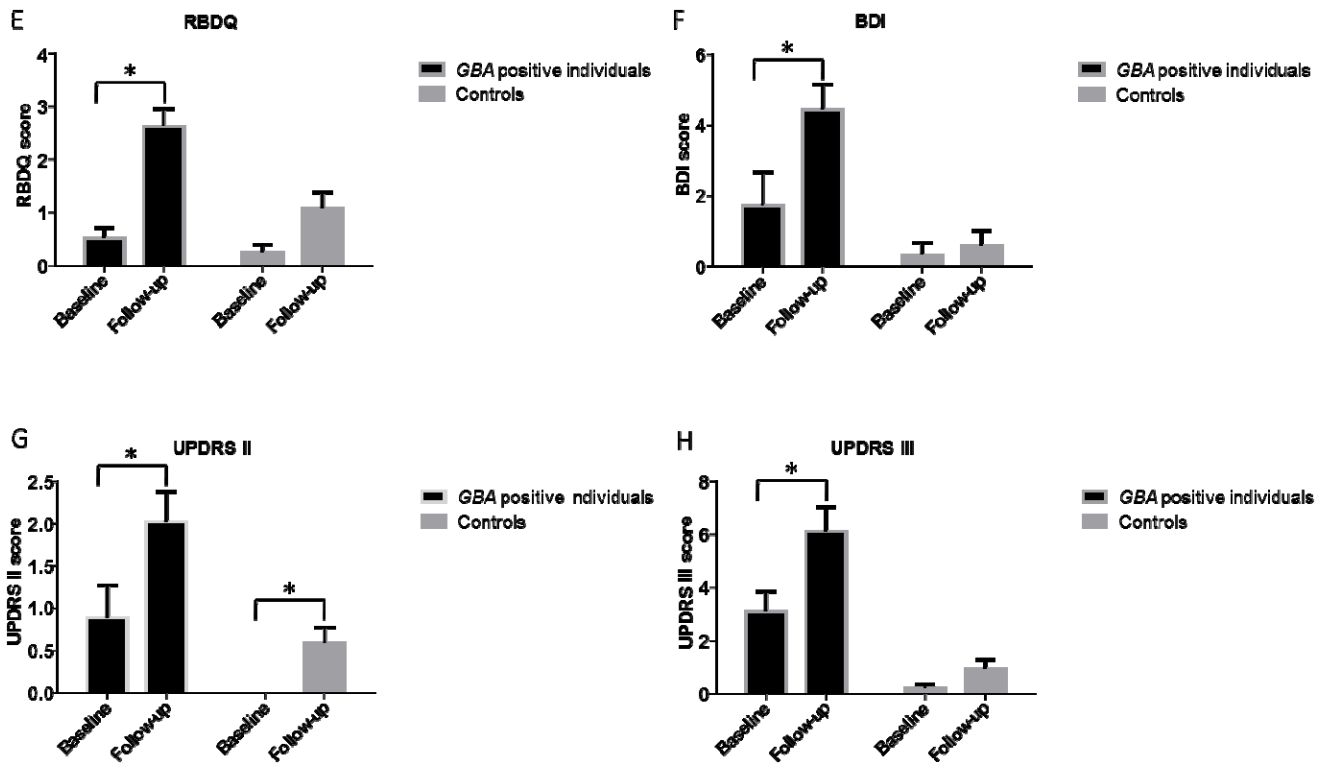
# Supplemental material

**Contents:**




## eFigure 1. Clinical markers in a pooled analysis comparing all *GBA* mutation positive individuals versus controls.

Figures demonstrate mean baseline and follow-up UPSIT scores (A), mean baseline and follow-up UMSARS scores (B), mean baseline and follow-up MoCA scores (C), and mean baseline and follow-up MMSE scores (D) for *GBA* positive individuals compared to controls. Means are plotted together with the SEM.




## eFigure 2. Clinical markers in a pooled analysis comparing all *GBA* mutation positive individuals versus controls.

Figures demonstrate a statistically significant increase in mean follow-up RBDQ (E), depression (F), and UPDRS III (H) scores in *GBA* mutation positive individuals compared to controls, and mean baseline and follow-up UPDRS II scores in *GBA* mutation positive individuals and controls (G). Means are plotted together with the SEM.

**eTable 1. Two year follow-up data when *GBA* mutation positive individuals with parkinsonian signs are excluded.**

| | | Type 1 GD patients (n=26) | Heterozygous *GBA* mutation carriers (n=26) | Controls (n=26) | *P* (between)[b] | | |
|---|---|---|---|---|---|---|---|
| | | | | | $P^1$ | $P^2$ | $P^3$ |
| **UPSIT** | Baseline | 32·71 (1·09) | 31·68 (0·89) | 35·32 (0·40) | | | |
| | Follow-up | 31·29 (1·13) | 30·68 (1·15) | 33·95 (0·62) | ·001[c] | ·001[c] | ·96 |
| | *P* (within) [a] | ·03 | ·27 | ·13 | | | |
| **UMSARS** | Baseline | 0·31 (0·14) | 0·39 (0·16) | 0·08 (0·06) | | | |
| | Follow-up | 0·42 (0·13) | 0·46 (0·15) | 0·13 (0·07) | ·14 | ·05 | 1·00 |
| | *P* (within) [a] | ·32 | ·90 | ·32 | | | |
| **RBDQ** | Baseline | 0·88 (0·31) | 0·11 (0·11) | 0·25 (0·14) | | | |
| | Follow-up | 2·96 (0·62) | 2·36 (0·42) | 1·08 (0·30) | ·34 | 1·00 | ·32 |
| | *P* (within) [a] | <·001[c] | <·001[c] | ·07 | | | |
| **MMSE** | Baseline | 29·23 (0·16) | 29·29 (0·19) | 29·28 (0·16) | | | |
| | Follow-up | 28·42 (0·54) | 28·71 (0·33) | 29·50 (0·21) | ·001[c] | ·006[c] | 1·00 |
| | *P* (within) [a] | ·09 | ·11 | ·30 | | | |
| **MoCA** | Baseline | 26·23 (0·56) | 25·93 (0·55) | 27·32 (0·23) | <·001[c] | | 1·00 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Follow-up | 26·42 (0·83) | 26·44 (0·55) | 27·73 (0·26) | | | <·001[c] |
| | *P* (within)[a] | ·70 | ·13 | ·20 | | | |
| | | **Type 1 GD patients (n=26)** | **Heterozygous *GBA* mutation carriers (n=26)** | **Controls (n=26)** | ***P* (between)[b]** | | |
| | | | | | ***P*[1]** | ***P*[2]** | ***P*[3]** |
| **UPDRS II** | Baseline | 1·44 (0·96) | 0.36 (0·23) | 0·00 (0·00) | | | |
| | Follow-up | 2.16 (0·65) | 1·29 (0·32) | 0·58 (0·19) | ·04 | 1·00 | ·009[c] |
| | *P* (within)[a] | ·01[c] | ·001[c] | ·006[c] | | | |
| **UPDRS III** | Baseline | 2·29 (0·62) | 1·32 (0·43) | 0·21 (0·17) | | | |
| | Follow-up | 5·29 (1·25) | 3·79 (0·59) | 0·92 (0·37) | <·001[c] | ·05 | ·07 |
| | *P* (within)[a] | ·001[c] | <·001[c] | ·06 | | | |
| **BDI** | Baseline | 3·00 (1·99) | 0·65 (0·41) | 0·33 (0·33) | | | |
| | Follow-up | 5·65 (1·27) | 2·88 (0·68) | 0·58 (0·43) | ·15 | 1·00 | ·04 |
| | *P* (within)[a] | ·10 | ·01[c] | ·11 | | | |

Abbreviations: *UPSIT* Smell Identification Test, *UMSARS* Unified Multiple System Atrophy Rating Scale, *MoCA* Montreal Cognitive assessment, *MMSE* Mini-Mental State Examination, *RBDQ* Rapid Eye Movement Sleep Behaviour Disorder Questionnaire, *UPDRS* Unified Parkinson's Disease Rating Scale, *BDI* Becks Depression Inventory.

Results are presented as mean and SEM. Significance was taken at the 5% level for all variables. Only values which survived multiple comparisons with the FDR procedure were denoted significant.

Reported *P* values compare the mean values for clinical markers within groups (baseline and follow-up) and between groups (Type 1 GD, carriers and controls) at follow-up.

[1] Controls versus Type 1 GD patients.
[2] Controls versus heterozygote *GBA* mutation carriers.
[3] Type 1 GD patients versus heterozygote *GBA* mutation carriers.

[a] Paired t-test.
[b] Two-way ANCOVA with Bonferroni correction.
[c] Statistically significant difference.

## eTable 2. Demographic, clinical and genetic characteristics of *GBA* mutation positive individuals with parkinsonism versus those without parkinsonism.

| | ***GBA* mutation positive individuals** | | |
|---|---|---|---|
| | **Parkinsonism* (n=6)** | **No parkinsonism (n=52)** | ***P* value** |
| Age, years | 74·3 (3·2) | 59·9 (1·5) | ·002[ac] |
| Gender (F/M) | 1/5 | 26/26 | ·14[b] |
| Ethnicity (Ashkenazi/White British) | 3/3 | 3/7 | ·17[b] |
| Family history of PD, % | 0 | 13·5 | ·32 |
| Most frequent *GBA* allele | N370S | N370S | - |

Results are presented as mean and SEM. Significance was taken at the 5% level.
Abbreviations: *ERT* Enzyme Replacement Therapy. *SRT* Substrate Reduction Therapy.
*Patients without Parkinson disease but with subtle evolving features of parkinsonism.
[a] One-way ANOVA.
[b] Chi-squared test.
[c] Statistically significant difference.

## eTable 3. Baseline and follow-up clinical markers in a comparison of *GBA* mutation positive individuals with parkinsonism and *GBA* mutation positive individuals without parkinsonism.

| | | ***GBA* mutation positive individuals** | | ***P* (between)[b]** |
|---|---|---|---|---|
| | | **Parkinsonism* (n=6)** | **No parkinsonism (n=52)** | ***P*[1]** |
| **UPSIT** | Baseline | 29·2 (2·1) | 32·2 (0·7) | ·16 |
| | Follow-up | 28·7 (1·6) | 31·0 (0·8) | |
| | *P* (within) [a] | ·67 | ·02 | |

| | | | | |
|---|---|---|---|---|
| **UMSARS** | Baseline | 0·7 (0·5) | 0·4 (0·1) | ·37 |
| | Follow-up | 1·8 (0·5) | 0·4 (0·1) | |
| | *P* (within) [a] | ·10 | ·48 | |
| **RBDQ** | Baseline | 0·8 (0·8) | 0·5 (0·2) | ·60 |
| | Follow-up | 2·5 (0·9) | 2·6 (0·4) | |
| | *P* (within) [a] | ·04 | <·001 [c] | |

| | | ***GBA* mutation positive individuals** | | ***P* (between)[b]** |
|---|---|---|---|---|
| | | **Parkinsonism* (n=6)** | **No parkinsonism (n=52)** | ***P*[1]** |
| **MMSE** | Baseline | 29·0 (0·5) | 29·3 (0·1) | ·52 |
| | Follow-up | 28·0 (0·7) | 28·6 (0·3) | |
| | *P* (within) [a] | ·10 | ·02 | |
| **MoCA** | Baseline | 22·8 (1·3) | 26·1 (0·4) | ·009 [c] |
| | Follow-up | 24·8 (1·7) | 26·4 (0·5) | |
| | *P* (within) [a] | ·07 | ·17 | |
| **UPDRS II** | Baseline | 1·0 (0·8) | 0·9 (0·4) | ·92 |
| | Follow-up | 4·8 (1·4) | 1·7 (0·3) | |
| | *P* (within) [a] | ·03 | <·001 [c] | |

| | | | | |
|---|---|---|---|---|
| **UPDRS III** | Baseline | 14·5 (4·1) | 1·8 (0·4) | <·001[c] |
| | Follow-up | 20·2 (4·3) | 4·5 (0·6) | |
| | *P* (within) [a] | ·04 | <·001[c] | |
| **BDI** | Baseline | 0·0 (0·0) | 1·8 (1·0) | ·66 |
| | Follow-up | 7·5 (0·5) | 4·3 (0·7) | |
| | | ·18 | ·005[c] | |

Abbreviations: *UPSIT* Smell Identification Test, *UMSARS* Unified Multiple System Atrophy Rating Scale, *MoCA* Montreal Cognitive assessment, *MMSE* Mini-Mental State Examination, *RBDQ* Rapid Eye Movement Sleep Behaviour Disorder Questionnaire, *UPDRS* Unified Parkinson's Disease Rating Scale, *BDI* Becks Depression Inventory.

*Patients without Parkinson disease but with subtle evolving features of parkinsonism.

Results are presented as mean and SEM. Significance was taken at the 5% level for all variables. Only values which survived multiple comparisons with the FDR procedure were denoted significant.

Reported *P* values compare the mean values for clinical markers within groups (baseline and follow-up) and between groups (parkinsonism and no parkinsonism) at baseline.

[1] Parkinsonism versus no parkinsonism.
[a] Paired t-test.
[b] One-way ANOVA with Bonferroni correction.
[c] Statistically significant difference.