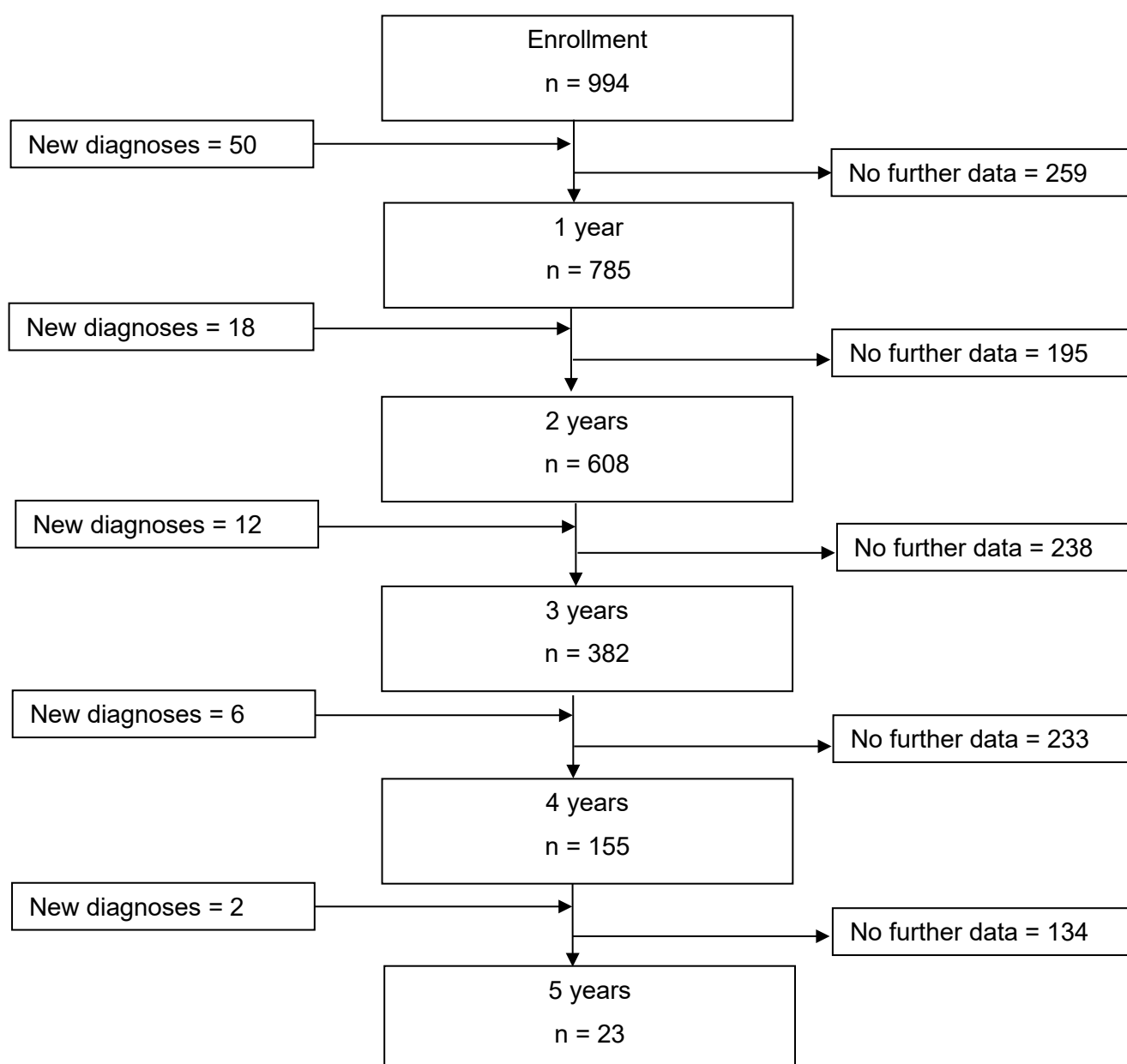


## SUPPLEMENTARY MATERIAL

### Appendix 1: Supplementary Figure

Flow diagram indicating sample sizes across time points (patients diagnosed with Huntington disease on the basis of clinician confidence  $\geq 99\%$  in diagnosis according to UHDRS motor criteria and CAG counts greater than 35).



**Appendix 2: Trajectory of Apathy over Time**

**Table 1**

*Linear mixed model examining the trajectory of apathy over time*

<b>Parameter</b>	<b>Estimate</b>	<b>95% CI</b>	<b>Sig</b>
<b>Apathy over time</b>			
Intercept <sup>1</sup>	3.33	0.06, 6.61	0.046
Time effect <sup>2</sup>	0.10	0.05, 0.14	<b>&lt; 0.001</b>
CAG	-0.03	-0.08, 0.03	0.325
Age	-0.01	-0.03, 0.01	0.328
Sex (female)	0.09	-0.24, 0.41	0.593
<b>Controlling for depression and medications</b>			
Intercept <sup>3</sup>	1.36	-2.00, 4.72	0.427
Time effect <sup>4</sup>	0.07	0.03, 0.11	<b>0.002</b>
CAG	-0.01	-0.07, 0.05	0.710
Age	0.00	-0.02, 0.02	0.873
Sex (female)	-0.28	-0.61, 0.04	0.086
Depression	0.42	0.37, 0.46	<b>&lt; 0.001</b>
Antidepressant	0.33	0.03, 0.64	<b>0.034</b>
Stimulant	-0.31	-1.42, 0.79	0.580
Antipsychotic	0.84	0.51, 1.17	<b>&lt; 0.001</b>

*Note.* Apathy and depression were measured using the Unified Huntington Disease Rating Scale (UHDRS). Numbers in bold indicate p-values < 0.05.

<sup>1</sup>Random effect with mean 3.33 and SD = 1.71

<sup>2</sup>Random effect with mean 0.10 and SD = 0.17

<sup>3</sup>Random effect with mean 1.36 and SD = 1.34

<sup>4</sup>Random effect with mean 0.07 and SD = 0.17

**Table 2**

*Linear mixed model examining the trajectory of depression*

Parameter	Estimate	95% CI	Sig
<b>Depression over time</b>			
Intercept <sup>1</sup>	6.23	3.51, 8.95	<b>&lt; 0.001</b>
Time effect <sup>2</sup>	-0.01	-0.04, 0.02	0.610
CAG	-0.07	-0.12, -0.03	<b>0.002</b>
Age	-0.03	-0.05, -0.01	<b>&lt; 0.001</b>
Sex (female)	0.64	0.38, 0.91	<b>&lt; 0.001</b>
<b>Controlling for apathy and medications</b>			
Intercept <sup>3</sup>	4.98	2.20, 7.76	<b>&lt; 0.001</b>
Time effect <sup>4</sup>	-0.04	-0.07, 0.00	<b>0.029</b>
CAG	-0.06	-0.11, -0.01	<b>0.015</b>
Age	-0.03	-0.04, -0.01	<b>0.001</b>
Sex (female)	0.65	0.38, 0.91	<b>&lt; 0.001</b>
Apathy	0.26	0.23, 0.28	<b>&lt; 0.001</b>
Antidepressant	0.29	0.05, 0.54	<b>0.019</b>
Stimulant	0.31	-0.54, 1.17	0.471
Antipsychotic	-0.12	-0.38, 0.15	0.385

*Note.* Apathy and depression were measured using the Unified Huntington Disease Rating Scale (UHDRS). Numbers in bold indicate p-values < 0.05.

<sup>1</sup>Random effect with mean 6.23 and SD = 1.67

<sup>2</sup>Random effect with mean -0.01 and SD = 0.00

<sup>3</sup>Random effect with mean 4.98 and SD = 1.39

<sup>4</sup>Random effect with mean -0.04 and SD = 0.05

**Appendix 3: Trajectory of Apathy over Time****Table 1***Unadjusted mean scores of apathy and depression across the first four years of the study*

	<b>Apathy</b>	<b>Depression</b>
<b>Baseline</b>	1.96 (3.45)	1.71 (2.95)
<b>1 year</b>	2.18 (3.67)	1.62 (2.88)
<b>2 years</b>	1.99 (3.36)	1.49 (2.61)
<b>3 years</b>	2.50 (3.86)	1.75 (2.87)
<b>4 years</b>	2.71 (4.05)	1.56 (2.66)

*Note.* Apathy and depression were measured using the Unified Huntington Disease Rating Scale (UHDRS). Characteristics are summarized as means (standard deviations). Analyses focused on the first four years of the study due to the small number of participants returning thereafter (see main text).

**Appendix 4: Subdomain Outcomes**

**Table 1**

*Linear mixed models for cognitive tests other than the Mini-Mental State Examination*

<b>Parameter</b>	<b>Estimate</b>	<b>95% CI</b>	<b>Sig</b>
<b>Symbol Digit Modalities Test</b>			
Intercept <sup>1</sup>	133.13	118.63, 147.62	< 0.001
Time effect <sup>2</sup>	-1.32	-1.45, -1.18	< 0.001
Apathy	-0.13	-0.21, -0.05	0.001
Depression	-0.05	-0.15, 0.04	0.265
CAG	-1.75	-2.00, -1.50	< 0.001
Age	-0.53	-0.61, -0.45	< 0.001
Sex (female)	0.30	-0.97, 1.57	0.647
<b>Verbal Fluency</b>			
Intercept <sup>3</sup>	117.40	100.91, 133.90	< 0.001
Time effect <sup>4</sup>	-0.62	-0.76, -0.48	< 0.001
Apathy	-0.18	-0.27, -0.09	< 0.001
Depression	0.12	0.01, 0.23	0.026
CAG	-1.64	-1.93, -1.36	< 0.001
Age	-0.39	-0.48, -0.30	< 0.001
Sex (female)	0.21	-1.25, 1.66	0.780
<b>Stroop Interference Test</b>			
Intercept <sup>5</sup>	103.44	89.30, 117.58	< 0.001
Time effect <sup>6</sup>	-0.97	-1.12, -0.83	< 0.001
Apathy	-0.39	-0.54, -0.25	< 0.001
Apathy*Time	0.03	0.01, 0.05	0.003
Depression	-0.04	-0.15, 0.07	0.457
CAG	-1.11	-1.36, -0.87	< 0.001

Age	-0.48	-0.56, -0.40	<b>&lt; 0.001</b>
Sex (female)	0.30	-0.95, 1.55	0.642

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*Note.* Apathy and depression were measured using the Unified Huntington Disease Rating Scale (UHDRS). Numbers in bold indicate p-values < 0.05.

<sup>1</sup> *Random effect with mean 133.13 and SD = 9.03*

<sup>2</sup> *Random effect with mean -1.32 and SD = 0.75*

<sup>3</sup> *Random effect with mean 117.40 and SD = 10.90*

<sup>4</sup> *Random effect with mean -0.62 and SD = 0.59*

<sup>5</sup> *Random effect with mean 103.44 and SD = 8.99*

<sup>6</sup> *Random effect with mean -0.97 and SD = 0.58*

**Table 2**

*Linear mixed models for occupational functioning, suicidal ideation, and psychosis*

<b>Parameter</b>	<b>Estimate</b>	<b>95% CI</b>	<b>Sig</b>
<b>Occupational Functioning</b>			
Intercept <sup>1</sup>	5.17	4.16, 6.18	< 0.001
Time effect <sup>2</sup>	-0.10	-0.11, -0.09	< 0.001
Apathy	-0.03	-0.05, -0.02	< 0.001
Apathy*Time	0.00	0.00, 0.00	< 0.001
Depression	-0.01	-0.02, 0.01	0.321
CAG	-0.06	-0.08, -0.05	< 0.001
Age	-0.02	-0.02, -0.01	< 0.001
Sex (female)	-0.08	-0.18, 0.02	0.097
<b>Suicidal Ideation</b>			
Intercept <sup>3</sup>	-0.75	-1.73, 0.24	0.138
Time effect <sup>4</sup>	-0.01	-0.02, 0.00	0.154
Apathy	0.01	-0.01, 0.02	0.326
Depression	0.09	0.08, 0.11	< 0.001
Independence	0.00	0.00, 0.00	0.784
Cognition	-0.01	-0.02, 0.00	0.303
Motor	0.00	0.00, 0.00	0.284
CAG	0.02	0.00, 0.03	0.054
Age	0.00	0.00, 0.01	0.523
Sex (female)	-0.02	-0.09, 0.05	0.559
Antidepressant	0.05	-0.02, 0.13	0.148
<b>Psychosis</b>			
Intercept <sup>5</sup>	-1.42	-3.22, 0.38	0.123
Time effect <sup>6</sup>	-0.02	-0.04, 0.01	0.193

Apathy	0.02	0.00, 0.04	<b>0.026</b>
Depression	0.05	0.03, 0.08	<b>&lt; 0.001</b>
CAG	0.03	-0.01, 0.06	0.107
Age	0.01	0.00, 0.02	0.173
Sex (female)	-0.01	-0.19, 0.17	0.927
Antipsychotic	0.54	0.37, 0.72	<b>&lt; 0.001</b>

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*Note.* Independence, occupational functioning, and neuropsychiatric symptoms were measured using the Unified Huntington Disease Rating Scale (UHDRS). Psychosis was calculated as the sum of the total scores of delusions and hallucinations within the UHDRS. Numbers in bold indicate p-values < 0.05.

<sup>1</sup>Random effect with mean 5.17 and SD = 0.74

<sup>2</sup>Random effect with mean -0.10 and SD = 0.01

<sup>3</sup>Random effect with mean -0.75 and SD = 0.17

<sup>4</sup>Random effect with mean -0.01 and SD = 0.00

<sup>5</sup>Random effect with mean -1.42 and SD = 0.15

<sup>6</sup>Random effect with mean -0.02 and SD = 0.00



**Table 3**

*Linear mixed models for measures of individual motor symptoms*

<b>Parameter</b>	<b>Estimate</b>	<b>95% CI</b>	<b>Sig</b>
<b>Chorea</b>			
Intercept <sup>1</sup>	-2.75	-8.18, 2.67	0.319
Time effect <sup>2</sup>	0.20	0.14, 0.27	<b>&lt; 0.001</b>
Apathy	-0.02	-0.07, 0.02	0.294
Depression	0.01	-0.04, 0.07	0.670
CAG	0.16	0.07, 0.25	<b>0.001</b>
Age	0.10	0.06, 0.13	<b>&lt; 0.001</b>
Sex (female)	0.01	-0.53, 0.55	0.979
Antipsychotic	0.01	-0.43, 0.46	0.953
Tetrabenazine	0.38	-0.35, 1.11	0.305
<b>Dystonia</b>			
Intercept <sup>3</sup>	-15.43	-19.14, -11.71	<b>&lt; 0.001</b>
Time effect <sup>4</sup>	0.30	0.24, 0.35	<b>&lt; 0.001</b>
Apathy	0.02	-0.01, 0.05	0.274
Depression	0.01	-0.03, 0.05	0.525
CAG	0.32	0.25, 0.38	<b>&lt; 0.001</b>
Age	0.07	0.05, 0.09	<b>&lt; 0.001</b>
Sex (female)	-0.03	-0.40, 0.34	0.870
Antipsychotic	0.53	0.22, 0.85	<b>0.001</b>
Tetrabenazine	-0.32	-0.85, 0.21	0.243
<b>Rigidity</b>			
Intercept <sup>5</sup>	-5.48	-7.04, -3.93	<b>&lt; 0.001</b>
Time effect <sup>6</sup>	0.10	0.08, 0.12	<b>&lt; 0.001</b>
Apathy	0.02	0.00, 0.03	<b>0.032</b>

Depression	0.01	-0.01, 0.03	0.391
CAG	0.12	0.10, 0.15	<b>&lt; 0.001</b>
Age	0.02	0.01, 0.03	<b>&lt; 0.001</b>
Sex (female)	-0.17	-0.32, -0.01	<b>0.035</b>
Antipsychotic	0.16	0.03, 0.30	<b>0.020</b>
Tetrabenazine	0.01	-0.22, 0.24	0.930
<b>Balance</b>			
Intercept <sup>7</sup>	-16.32	-18.88, -13.77	<b>&lt; 0.001</b>
Time effect <sup>8</sup>	0.32	0.29, 0.35	<b>&lt; 0.001</b>
Apathy	0.03	0.01, 0.05	<b>0.004</b>
Depression	0.02	0.00, 0.05	<b>0.042</b>
CAG	0.29	0.24, 0.33	<b>&lt; 0.001</b>
Age	0.11	0.09, 0.12	<b>&lt; 0.001</b>
Sex (female)	0.85	0.59, 1.11	<b>&lt; 0.001</b>
Antipsychotic	0.64	0.44, 0.83	<b>&lt; 0.001</b>
Tetrabenazine	0.58	0.26, 0.90	<b>&lt; 0.001</b>
<b>Bradykinesia</b>			
Intercept <sup>9</sup>	-4.78	-5.84, -3.72	<b>&lt; 0.001</b>
Time effect <sup>10</sup>	0.09	0.08, 0.10	<b>&lt; 0.001</b>
Apathy	0.02	0.01, 0.02	<b>0.001</b>
Depression	0.01	0.00, 0.02	0.182
CAG	0.10	0.08, 0.12	<b>&lt; 0.001</b>
Age	0.02	0.01, 0.03	<b>&lt; 0.001</b>
Sex (female)	-0.02	-0.13, 0.08	0.668
Antipsychotic	0.27	0.18, 0.36	<b>&lt; 0.001</b>
Tetrabenazine	0.13	-0.01, 0.28	0.076

*Note.* Movement disturbances and neuropsychiatric symptoms were measured using the Unified Huntington Disease Rating Scale (UHDRS). Numbers in bold indicate p-values < 0.05.

<sup>1</sup>Random effect with mean -2.75 and SD = 3.70

<sup>2</sup>Random effect with mean 0.20 and SD = 0.26

<sup>3</sup>Random effect with mean -15.43 and SD = 2.21

<sup>4</sup>Random effect with mean 0.30 and SD = 0.32

<sup>5</sup>Random effect with mean -5.48 and SD = 0.93

<sup>6</sup>Random effect with mean 0.10 and SD = 0.11

<sup>7</sup>Random effect with mean -16.32 and SD = 1.74

<sup>8</sup>Random effect with mean 0.32 and SD = 0.17

<sup>9</sup>Random effect with mean -4.78 and SD = 0.69

<sup>10</sup>Random effect with mean 0.09 and SD = 0.06

**Appendix 5: Apathy as Dichotomous Trait**

**Table 1**

*Linear mixed models for measures of function*

<b>Parameter</b>	<b>Estimate</b>	<b>95% CI</b>	<b>Sig</b>
<b>Independence Scale</b>			
Intercept <sup>1</sup>	170.75	155.29, 186.22	<b>&lt; 0.001</b>
Time effect <sup>2</sup>	-2.38	-2.56, -2.19	<b>&lt; 0.001</b>
Apathy	-4.03	-4.97, -3.08	<b>&lt; 0.001</b>
Depression	-0.57	-1.61, 0.47	0.281
CAG	-1.33	-1.59, -1.07	<b>&lt; 0.001</b>
Age	-0.38	-0.47, -0.29	<b>&lt; 0.001</b>
Sex (female)	-2.61	-4.15, -1.06	<b>0.001</b>
<b>Total Functional Capacity</b>			
Intercept <sup>3</sup>	27.09	23.72, 30.46	<b>&lt; 0.001</b>
Time effect for apathy <sup>*4</sup>	-0.43	-0.47, -0.39	<b>&lt; 0.001</b>
Time effect for no apathy <sup>*5</sup>	-0.49	-0.53, -0.45	<b>&lt; 0.001</b>
Apathy at time of diagnosis	-0.98	-1.26, -0.69	<b>&lt; 0.001</b>
Depression	-0.03	-0.24, 0.19	0.816
CAG	-0.28	-0.34, -0.22	<b>&lt; 0.001</b>
Age	-0.08	-0.10, -0.06	<b>&lt; 0.001</b>
Sex (female)	-0.60	-0.94, -0.27	<b>&lt; 0.001</b>

*Note.* Function and neuropsychiatric symptoms were measured using the Unified Huntington Disease Rating Scale (UHDRS). Numbers in bold indicate p-values < 0.05.

\*Interaction significant at p = 0.06. Separate time effects reported for different values of categorical variable.

<sup>1</sup>Random effect with mean 170.75 and SD = 10.46

<sup>2</sup>Random effect with mean -2.38 and SD = 1.28

<sup>3</sup>Random effect with mean 27.09 and SD = 2.41

<sup>4</sup>Random effect with mean -0.43 and SD = 0.22

<sup>5</sup>Random effect with mean -0.49 and SD = 0.22

**Table 2**

*Linear mixed models for measures of cognition*

<b>Parameter</b>	<b>Estimate</b>	<b>95% CI</b>	<b>Sig</b>
<b>Mini-Mental State Examination</b>			
Intercept <sup>1</sup>	46.15	41.58, 50.72	< 0.001
Time effect for apathy <sup>*2</sup>	-0.44	-0.51, -0.37	< 0.001
Time effect for no apathy <sup>*3</sup>	-0.38	-0.45, -0.30	< 0.001
Apathy at time of diagnosis	-0.38	-0.83, 0.08	0.108
Depression	-0.06	-0.40, 0.29	0.741
CAG	-0.33	-0.41, -0.25	< 0.001
Age	-0.09	-0.12, -0.06	< 0.001
Sex (female)	-0.41	-0.86, 0.04	0.073
<b>Symbol Digit Modalities Test</b>			
Intercept <sup>4</sup>	135.82	121.20, 150.44	< 0.001
Time effect <sup>5</sup>	-1.21	-1.35, -1.07	< 0.001
Apathy	-1.64	-2.36, -0.92	< 0.001
Depression	-0.30	-1.09, 0.50	0.469
CAG	-1.79	-2.04, -1.53	< 0.001
Age	-0.54	-0.62, -0.46	< 0.001
Sex (female)	0.33	-0.94, 1.59	0.615
<b>Verbal Fluency</b>			
Intercept <sup>6</sup>	118.09	101.39, 134.78	< 0.001
Time effect <sup>7</sup>	-0.60	-0.75, -0.45	< 0.001
Apathy	-1.17	-2.00, -0.34	<b>0.006</b>
Depression	0.56	-0.37, 1.48	0.237
CAG	-1.65	-1.94, -1.36	< 0.001
Age	-0.40	-0.49, -0.30	< 0.001

Sex (female)	0.25	-1.21, 1.70	0.741
<b>Stroop Interference Test</b>			
Intercept <sup>8</sup>	106.02	91.63, 120.41	<b>&lt; 0.001</b>
Time effect <sup>9</sup>	-0.83	-0.97, -0.68	<b>&lt; 0.001</b>
Apathy	-1.60	-2.41, -0.80	<b>&lt; 0.001</b>
Depression	-0.73	-1.62, 0.16	0.107
CAG	-1.16	-1.40, -0.91	<b>&lt; 0.001</b>
Age	-0.49	-0.58, -0.41	<b>&lt; 0.001</b>
Sex (female)	0.35	-0.90, 1.61	0.581

*Note.* Neuropsychiatric symptoms were measured using the Unified Huntington Disease Rating Scale (UHDRS). Numbers in bold indicate p-values < 0.05.

\*Interaction significant at p = 0.97. Separate time effects reported for different values of categorical variable.

<sup>1</sup>Random effect with mean 46.15 and SD = 2.75

<sup>2</sup>Random effect with mean -0.44 and SD = 0.46

<sup>3</sup>Random effect with mean -0.38 and SD = 0.46

<sup>4</sup>Random effect with mean 135.82 and SD = 9.04

<sup>5</sup>Random effect with mean -1.21 and SD = 0.74

<sup>6</sup>Random effect with mean 118.09 and SD = 10.90

<sup>7</sup>Random effect with mean -0.60 and SD = 0.60

<sup>8</sup>Random effect with mean 106.02 and SD = 9.03

<sup>9</sup>Random effect with mean -0.83 and SD = 0.59

**Table 3**

*Linear mixed models for measures of motor and behavioral symptoms*

<b>Parameter</b>	<b>Estimate</b>	<b>95% CI</b>	<b>Sig</b>
<b>Motor Total</b>			
Intercept <sup>1</sup>	-92.92	-110.91, -74.94	<b>&lt; 0.001</b>
Time effect <sup>2</sup>	2.38	2.16, 2.59	<b>&lt; 0.001</b>
Apathy	1.44	0.35, 2.53	<b>0.010</b>
Depression	0.44	-0.76, 1.63	0.474
CAG	2.04	1.73, 2.34	<b>&lt; 0.001</b>
Age	0.57	0.46, 0.68	<b>&lt; 0.001</b>
Sex (female)	1.84	0.04, 3.63	<b>0.045</b>
Antipsychotic	2.75	1.53, 3.96	<b>&lt; 0.001</b>
Tetrabenazine	1.52	-0.42, 3.47	0.124
<b>Neuropsychiatric Symptoms</b>			
Intercept <sup>3</sup>	0.06	-11.48, 11.60	0.992
Time effect <sup>4</sup>	-0.25	-0.38, -0.12	<b>&lt; 0.001</b>
Apathy	5.21	4.20, 6.21	<b>&lt; 0.001</b>
Depression	4.55	3.49, 5.61	<b>&lt; 0.001</b>
CAG	0.13	-0.07, 0.32	0.209
Age	-0.02	-0.09, 0.05	0.656
Sex (female)	0.47	-0.65, 1.58	0.411
Antipsychotic	2.19	1.16, 3.22	<b>&lt; 0.001</b>

*Note.* Movement disturbances and neuropsychiatric symptoms were measured using the Unified Huntington Disease Rating Scale (UHDRS). Numbers in bold indicate p-values < 0.05.

<sup>1</sup>Random effect with mean -92.92 and SD = 12.32

<sup>2</sup>Random effect with mean 2.38 and SD = 1.42

<sup>3</sup>Random effect with mean 0.06 and SD = 7.24

<sup>4</sup>Random effect with mean -0.25 and SD = 0.00

**Appendix 6: Baseline Apathy as a Predictor of Disease Course**

Apathy assessed as a continuous measure (score 0-16) at baseline; outcome measures assessed longitudinally across the study.

**Table 1**

*Linear mixed models for measures of function*

<b>Parameter</b>	<b>Estimate</b>	<b>95% CI</b>	<b>Sig</b>
<b>Independence Scale</b>			
Intercept <sup>1</sup>	169.23	153.79, 184.67	<b>&lt; 0.001</b>
Time effect <sup>2</sup>	-2.76	-2.97, -2.56	<b>&lt; 0.001</b>
Apathy	-1.09	-1.42, -0.77	<b>&lt; 0.001</b>
Apathy*Time	0.09	0.04, 0.14	<b>&lt; 0.001</b>
Depression	-0.12	-0.40, 0.17	0.422
CAG	-1.29	-1.56, -1.03	<b>&lt; 0.001</b>
Age	-0.37	-0.46, -0.27	<b>&lt; 0.001</b>
Sex (female)	-2.76	-4.32, -1.20	<b>0.001</b>
<b>Total Functional Capacity</b>			
Intercept <sup>3</sup>	26.84	23.50, 30.19	<b>&lt; 0.001</b>
Time effect <sup>4</sup>	-0.53	-0.57, -0.49	<b>&lt; 0.001</b>
Apathy	-0.24	-0.31, -0.17	<b>&lt; 0.001</b>
Apathy*Time	0.02	0.01, 0.03	<b>&lt; 0.001</b>
Depression	0.00	-0.06, 0.06	0.947
CAG	-0.27	-0.33, -0.22	<b>&lt; 0.001</b>
Age	-0.07	-0.10, -0.05	<b>&lt; 0.001</b>
Sex (female)	-0.65	-0.99, -0.31	<b>&lt; 0.001</b>

*Note.* Function and neuropsychiatric symptoms were measured using the Unified Huntington Disease Rating Scale (UHDRS). Numbers in bold indicate p-values < 0.05.

<sup>1</sup>Random effect with mean 169.23 and SD = 10.45

<sup>2</sup>Random effect with mean -2.76 and SD = 1.30



<sup>3</sup>*Random effect with mean 26.84 and SD = 2.38*

<sup>4</sup>*Random effect with mean -0.53 and SD = 0.23*

**Table 2**

*Linear mixed models for measures of cognition*

<b>Parameter</b>	<b>Estimate</b>	<b>95% CI</b>	<b>Sig</b>
<b>Mini-Mental State Examination</b>			
Intercept <sup>1</sup>	45.92	41.38, 50.46	< 0.001
Time effect <sup>2</sup>	-0.44	-0.50, -0.38	< 0.001
Apathy	-0.12	-0.19, -0.05	0.001
Depression	0.02	-0.06, 0.10	0.617
CAG	-0.32	-0.40, -0.25	< 0.001
Age	-0.08	-0.11, -0.06	< 0.001
Sex (female)	-0.46	-0.92, -0.01	0.045
<b>Symbol Digits Modalities Test</b>			
Intercept <sup>3</sup>	134.70	120.07, 149.34	< 0.001
Time effect <sup>4</sup>	-1.43	-1.58, -1.28	< 0.001
Apathy	-0.47	-0.74, -0.19	0.001
Apathy*Time	0.06	0.02, 0.10	0.005
Depression	-0.04	-0.28, 0.21	0.775
CAG	-1.76	-2.02, -1.51	< 0.001
Age	-0.53	-0.61, -0.45	< 0.001
Sex (female)	0.25	-1.03, 1.53	0.702
<b>Verbal Fluency</b>			
Intercept <sup>5</sup>	118.07	101.46, 134.68	< 0.001
Time effect <sup>6</sup>	-0.62	-0.77, -0.48	< 0.001
Apathy	-0.39	-0.63, -0.16	0.001
Depression	0.21	-0.06, 0.48	0.120
CAG	-1.65	-1.94, -1.36	< 0.001
Age	-0.39	-0.48, -0.30	< 0.001

Sex (female)	0.09	-1.38, 1.55	0.908
<b>Stroop Interference Test</b>			
Intercept <sup>7</sup>	104.72	90.46, 118.99	<b>&lt; 0.001</b>
Time effect <sup>8</sup>	-1.07	-1.23, -0.91	<b>&lt; 0.001</b>
Apathy	-0.74	-1.02, -0.45	<b>&lt; 0.001</b>
Depression	0.08	0.04, 0.12	<b>&lt; 0.001</b>
CAG	-0.01	-0.24, 0.22	0.933
Age	-1.12	-1.37, -0.88	<b>&lt; 0.001</b>
Sex (female)	-0.49	-0.57, -0.41	<b>&lt; 0.001</b>

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Note. Neuropsychiatric symptoms were measured using the Unified Huntington Disease Rating Scale (UHDRS). Numbers in bold indicate p-values < 0.05.

<sup>1</sup>Random effect with mean 45.92 and SD = 0.69

<sup>2</sup>Random effect with mean -0.44 and SD = 0.06

<sup>3</sup>Random effect with mean 134.70 and SD = 9.03

<sup>4</sup>Random effect with mean -1.43 and SD = 0.75

<sup>5</sup>Random effect with mean 118.07 and SD = 10.89

<sup>6</sup>Random effect with mean -0.62 and SD = 0.61

<sup>7</sup>Random effect with mean 104.72 and SD = 8.98

<sup>8</sup>Random effect with mean -1.07 and SD = 0.59

**Table 3**

*Linear mixed models for measures of neuropsychiatric and motor symptoms*

<b>Parameter</b>	<b>Estimate</b>	<b>95% CI</b>	<b>Sig</b>
<b>Motor Total</b>			
Intercept <sup>1</sup>	-91.48	-109.45, -73.51	<b>&lt; 0.001</b>
Time effect <sup>2</sup>	2.47	2.26, 2.68	<b>&lt; 0.001</b>
Apathy	0.17	-0.12, 0.46	0.262
Depression	0.12	-0.21, 0.44	0.485
CAG	2.02	1.71, 2.32	<b>&lt; 0.001</b>
Age	0.56	0.45, 0.67	<b>&lt; 0.001</b>
Sex (female)	1.84	0.03, 3.66	<b>0.047</b>
Antipsychotic	2.74	1.52, 3.96	<b>&lt; 0.001</b>
Tetrabenazine	1.59	-0.35, 3.53	0.109
<b>Neuropsychiatric Symptoms</b>			
Intercept <sup>3</sup>	5.89	-5.40, 17.18	0.306
Time effect <sup>4</sup>	0.13	-0.02, 0.28	0.092
Apathy	0.84	0.57, 1.11	<b>&lt; 0.001</b>
Apathy*Time	-0.07	-0.11, -0.04	<b>&lt; 0.001</b>
Depression	1.18	0.98, 1.39	<b>&lt; 0.001</b>
CAG	0.04	-0.15, 0.23	0.676
Age	-0.04	-0.10, 0.03	0.309
Sex (female)	0.30	-0.81, 1.40	0.600
Antipsychotic	2.08	1.04, 3.11	<b>&lt; 0.001</b>

*Note.* Movement disturbances and neuropsychiatric symptoms were measured using the Unified Huntington Disease Rating Scale (UHDRS). Numbers in bold indicate p-values < 0.05.

<sup>1</sup>Random effect with mean -91.48 and SD = 12.35

<sup>2</sup>Random effect with mean 2.47 and SD = 1.43

<sup>3</sup>Random effect with mean 5.89 and SD = 6.93

<sup>4</sup>Random effect with mean 0.13 and SD = 0.22