**Appendix E-1: Supplemental Data**

Table E1. Additional baseline characteristics by suicidal ideation/attempt status

|  |  |  |
| --- | --- | --- |
| Characteristic | No Suicidal Ideation/Attempt  (n = 557) | Suicidal Ideation/Attempt  (n = 52) |

|  |  |  |
| --- | --- | --- |
| At least 1 Behavioral item ≥ 2 | 382 (68.6%) | 41 (78.9%) |
| At least 1 Depressed Mood or Anxiety item ≥ 2 | 207 (37.2%) | 27 (51.9%) |
| At least 1 Irritable Behavior or Disruptive/Aggressive Behavior item ≥ 2 | 284 (51.0%) | 31 (59.6%) |
| At least 1 Suicidal Thoughts item ≥ 2 | 7 (1.3%) | 2 (3.9%) |
| Depressed Mood frequency (25a) ≥ 2 | 139 (25.0%) | 19 (36.5%) |
| Depressed Mood severity (25b) ≥ 2 | 145 (26.0%) | 24 (46.2%) |
| Low Self-Esteem/Guilt frequency (26a) ≥ 2 | 68 (12.2%) | 17 (32.7%) |
| Low Self-Esteem/Guilt severity (26b) ≥ 2 | 80 (14.4%) | 16 (30.8%) |
| Anxiety frequency (27a) ≥ 2 | 194 (34.8%) | 23 (44.2%) |
| Anxiety severity (27b) ≥ 2 | 172 (30.9%) | 21 (40.4%) |
| Suicidal Thoughts frequency (28a) ≥ 1 | 23 (4.1%) | 4 (7.7%) |
| Suicidal Thoughts severity (28b) ≥ 1 | 23 (4.1%) | 4 (7.7%) |
| Disruptive/Aggressive Behavior frequency (29a) ≥ 2 | 73 (13.1%) | 10 (19.2%) |
| Disruptive/Aggressive Behavior severity (29b) ≥ 2 | 26 (4.7%) | 5 (9.6%) |
| Irritable Behavior frequency (30a) ≥ 2 | 195 (35.0%) | 24 (46.2%) |
| Irritable Behavior severity (30b) ≥ 2 | 180 (32.3%) | 21 (40.4%) |
| Perseverative/Obsessional Thinking frequency (31a) ≥ 2 | 119 (21.4%) | 22 (42.3%) |
| Perseverative/Obsessional Thinking severity (31b) ≥ 2 | 127 (22.8%) | 20 (38.5%) |
| Compulsive Behavior frequency (32a) ≥ 2 | 66 (11.9%) | 9 (17.3%) |
| Compulsive Behavior severity (32b) ≥ 2 | 66 (11.9%) | 7 (13.5%) |
| Delusions frequency (33a) ≥ 2 | 14 (2.5%) | 3 (5.8%) |
| Delusions severity (33b) ≥ 2 | 12 (2.2%) | 2 (3.9%) |
| Hallucinations frequency (34a) ≥ 1 | 4 (0.7%) | 0 (0.0%) |
| Hallucinations severity (34b) ≥ 1 | 4 (0.7%) | 0 (0.0%) |
| Apathy frequency (35a) ≥ 2 | 130 (23.3%) | 16 (30.8%) |
| Apathy severity (35b) ≥ 2 | 123 (22.1%) | 17 (32.7%) |

Table E2. Associations between baseline variables and time to suicide attempt

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristic | Hazard Ratio | 95% CI | P-value |
| Age † | 0.78 | (0.57, 1.07) | 0.12 |
| Age at symptom onset † | 0.80 | (0.56, 1.14) | 0.21 |
| Age at HD diagnosis † | 0.82 | (0.60, 1.12) | 0.21 |
| Female Sex | 1.21 | (0.57, 2.58) | 0.62 |
| Marital status  Never married  Separated/widowed/divorced  Married | 1.00  0.64  0.62 | (0.21, 1.98)  (0.24, 1.59) | 0.59 |
| Education level ≤ high school | 1.45 | (0.66, 3.16) | 0.36 |
| Currently in the labor force | 0.94 | (0.41, 2.14) | 0.87 |
| History of tobacco abuse | 1.19 | (0.45, 3.15) | 0.73 |
| Active psychiatric diagnosis  Depression  Anxiety  Bipolar disorder  Depression or anxiety or bipolar disorder | 4.01  2.13  6.27  3.86 | (1.52, 10.59)  (0.99, 4.59)  (0.85, 46.29)  (1.33, 11.15) | 0.005  0.05  0.07  0.01 |
| Medication use  Antidepressant use  Anxiolytic use  Antidepressant or anxiolytic use | 2.73  1.16  2.46 | (1.10, 6.76)  (0.40, 3.36)  (0.99, 6.10) | 0.03  0.78  0.05 |
| Tetrabenazine use | 0.52 | (0.07, 3.81) | 0.52 |
| History of suicidal ideation | 2.01 | (0.81, 4.98) | 0.13 |
| Predictive genetic testing for HD | 2.18 | (1.01, 4.71) | 0.05 |
| CAG repeat length ‡ | 1.16 | (0.77, 1.75) | 0.47 |
| Coenzyme Q10 treatment | 1.28 | (0.60, 2.73) | 0.53 |

† Hazard ratio associated with a 10-year increase in age

‡ Hazard ratio associated with a 5-unit increase in CAG repeat length

History of alcohol abuse is not included because only 4 subjects reported having this history (and none of them had a suicide attempt)

Table E3. Associations between time-dependent variables and time to suicide attempt

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristic | Hazard Ratio | 95% CI | P-value |
| Body mass index (kg/m2) † | 0.85 | (0.57, 1.26) | 0.42 |
| Tetrabenazine use | 0.65 | (0.23, 1.89) | 0.43 |
| Total motor score † | 1.03 | (0.92, 1.15) | 0.63 |
| Total maximal dystonia score | 0.99 | (0.88, 1.11) | 0.85 |
| Total maximal chorea score | 1.07 | (0.99, 1.16) | 0.08 |
| Verbal Fluency Test † | 1.07 | (0.93, 1.24) | 0.35 |
| Symbol Digit Modalities Test † | 1.09 | (0.94, 1.26) | 0.26 |
| Stroop Interference Test – Color Naming † | 0.99 | (0.89, 1.11) | 0.90 |
| Stroop Interference Test – Word Reading † | 1.02 | (0.93, 1.11) | 0.70 |
| Stroop Interference Test – Interference † | 0.98 | (0.83, 1.16) | 0.82 |
| Behavioral Frequency score | 1.07 | (1.02, 1.13) | 0.01 |
| Behavioral Frequency × Severity score | 1.03 | (1.01, 1.05) | 0.003 |
| At least 1 Behavioral item ≥ 2 | 1.36 | (0.55, 3.37) | 0.51 |
| At least 1 Depressed Mood or Anxiety item ≥ 2 | 2.00 | (0.94, 4.28) | 0.07 |
| At least 1 Irritable Behavior or Disruptive/Aggressive Behavior item ≥ 2 | 1.46 | (0.67, 3.19) | 0.34 |
| At least 1 Suicidal Thoughts item ≥ 2 | 4.45 | (1.05, 18.80) | 0.04 |
| Functional Assessment score † | 0.86 | (0.57, 1.29) | 0.47 |
| Independence Scale score † | 1.02 | (0.87, 1.20) | 0.78 |
| Total Functional Capacity (TFC) score | 0.93 | (0.80, 1.07) | 0.29 |
| Worst value in an individual TFC domain  2  1  0 | 1.00  3.66  5.17 | (0.80, 16.75)  (1.14, 23.53) | 0.10 |

† Hazard ratio associated with a 5-unit increase in the variable

Table E4. Associations between individual behavioral items and time to suicide attempt

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristic | Hazard Ratio | 95% CI | P-value |
| Depressed Mood frequency (25a) ≥ 2 | 1.63 | (0.75, 3.57) | 0.22 |
| Depressed Mood severity (25b) ≥ 2 | 2.39 | (1.13, 5.10) | 0.02 |
| Low Self-Esteem/Guilt frequency (26a) ≥ 2 | 2.36 | (1.03, 5.40) | 0.04 |
| Low Self-Esteem/Guilt severity (26b) ≥ 2 | 3.04 | (1.39, 6.64) | 0.005 |
| Anxiety frequency (27a) ≥ 2 | 1.31 | (0.61, 2.82) | 0.49 |
| Anxiety severity (27b) ≥ 2 | 1.72 | (0.81, 3.68) | 0.16 |
| Suicidal Thoughts frequency (28a) ≥ 1 | 3.62 | (1.25, 10.48) | 0.02 |
| Suicidal Thoughts severity (28b) ≥ 1 | 3.66 | (1.26, 10.59) | 0.02 |
| Disruptive/Aggressive Behavior frequency (29a) ≥ 2 | 2.32 | (0.98, 5.48) | 0.06 |
| Disruptive/Aggressive Behavior severity (29b) ≥ 2 | 2.57 | (0.89, 7.45) | 0.08 |
| Irritable Behavior frequency (30a) ≥ 2 | 1.93 | (0.90, 4.10) | 0.09 |
| Irritable Behavior severity (30b) ≥ 2 | 1.52 | (0.71, 3.25) | 0.28 |
| Perseverative/Obsessional Thinking frequency (31a) ≥ 2 | 1.20 | (0.52, 2.74) | 0.67 |
| Perseverative/Obsessional Thinking severity (31b) ≥ 2 | 1.23 | (0.55, 2.74) | 0.62 |
| Compulsive Behavior frequency (32a) ≥ 2 | 1.25 | (0.43, 3.62) | 0.68 |
| Compulsive Behavior severity (32b) ≥ 2 | 1.61 | (0.61, 4.25) | 0.34 |
| Delusions frequency (33a) ≥ 2 | 2.68 | (0.63, 11.35) | 0.18 |
| Delusions severity (33b) ≥ 2 | 1.85 | (0.25, 13.65) | 0.55 |
| Apathy frequency (35a) ≥ 2 | 1.10 | (0.84, 1.45) | 0.50 |
| Apathy severity (35b) ≥ 2 | 1.18 | (0.85, 1.65) | 0.32 |

Hallucinations frequency and severity are not included because of the small number of people who experienced hallucinations

Table E5: Comparison of HD Suicidality in the Literature to that in 2CARE

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Reference | Design/Participants | Main Findings | Differences with 2CARE | Comment |
| [6] | Retrospective case/control  9 manifest HD subjects, 2 controls | Items more likely in those who completed suicide: having no offspring, family history of suicide, unmarried, connections to others with symptomatic HD, living alone, depression | Data regarding offspring, connectivity to other people with HD, family history of suicide, or living alone were not collected in 2CARE  No association in 2CARE between marital status and time to suicidal ideation or attempt | Only 5 completed suicides in 2CARE, prohibiting a meaningful comparison |
| [7] | Cross-sectional baseline, followed prospectively  152 HD subjects with varying disease severity | Suicidal ideation in 20% at baseline as measured by the Problem Behaviors Assessment (PBA), associated with depression, apathy, and use of antidepressants  After subjects were followed for 2 years, depression was the lone predictor of suicidal ideation | No association between suicidality and apathy seen in 2CARE | It is possible selection bias against apathy existed for the 2CARE cohort, due to participants being intrinsically motivated for participation in a long-term study  2CARE subjects were uniformly early in the course of their illness, whereas the greater heterogeneity of disease severity expected in a cross-sectional cohort might involve more behavioral heterogeneity |
| [8] | Prospective, observational  2106 REGISTRY participants, 98% with motor symptoms, all TFC stages | 8.0% suicidal ideation at baseline, 9.9% cumulative incidence after 4 years  At baseline, depression, prior suicide attempt, aggression, anxiety, and disease duration were associated with suicidal ideation  Depression (measured by the UHDRS) and benzodiazepine use were associated with suicidal ideation during follow-up | No significant association between aggression and suicidal ideation or attempt seen in 2CARE | Hubers et al. speculate on a paradoxical reaction to benzodiazepine use involving disinhibition, with potentially more suicidal risk resulting from use of these medications  Anxiolytic use alone was not associated with time to suicidal ideation or attempt in 2CARE. Hazard ratios for the disruptive/aggressive behavior items on the UHDRS were close to 2.0 (Table 4) but had wide confidence intervals  2CARE finding may reflect smaller, more homogenous cohort under study compared to this larger cohort |
| [3] | Retrospective  4171 HD subjects, varying disease severity | Critical suicide risk periods immediately before formal diagnosis and Stage II (TFC 7-10), when mounting disability may compound behavioral aspects of the disease | No association in 2CARE between time-dependent TFC score and suicidal ideation or attempt | All subjects in 2CARE at time of enrollment were essentially Stage I, with mean TFC scores in the placebo and coenzyme Q10 groups of 11.0 and 10.8, respectively  Given the length of follow-up in 2CARE and the annual TFC decline of approximately 1 point per year in participants with baseline TFC scores in the range of 7-13, the majority of subjects would be expected to enter Stage 2 or 3 longitudinally [9] |
| [10] | Retrospective  1941 HD subjects, HD Diagnosis Score of 2 or 3 | 26.5% with a history of suicidal ideation, 9.5% reported at least one suicide attempt [10]  Associated with concomitant depression (on UHDRS), anxiety, aggression, and irritability; more severe ideation associated with alcohol use | No association in 2CARE between aggressive behavior or history of alcohol abuse and suicidal ideation or attempt | 2CARE finding may be limited by low power; the hazard ratios for Disruptive/Aggressive Behavior (Table 4) approached 2.0 (with wide confidence intervals) and only four subjects had identified alcohol abuse during the study |
| [23] | Cross-sectional  5709 gene mutation carriers, 1220 pre-manifest and 4489 manifest (29.5% Stage I, 36.4% Stage II, 24.1% Stage III, 8% Stage IV, 2.1% Stage V) | 18.9% pre-manifest with history of ideation  27.3% manifest with history of ideation  Older age, single status, and unemployment associated with ideation in pre-manifest but not manifest group  Alcohol abuse associated with suicidality in pre-manifest group, drug abuse associated in manifest group  History of suicidal ideation, psychiatric co-morbidity, PBA-anxiety, PBA-depression, PBA-irritability, PBA-psychosis and PBA-apathy predictive of ideation in manifest group | Includes pre-manifest group  Much more heterogeneous manifest group (Stages I-V)  Cross-sectional, vs. longitudinal in 2CARE | Substantial numbers of subjects in similar Stage I and II range as 2CARE (1323, 1634 respectively)  Associations seen with alcohol and substance abuse, likely driven by larger sample  Depression, anxiety, irritability, prior suicidal ideation shared in common with 2CARE baseline variables  Depression, anxiety, irritability shared in common with 2CARE time-dependent associations |

**Appendix E-2: Participating Sites (Investigators and Coordinators):**

**All MD, DO and PhD participants listed served as co-investigators, and were responsible for recruitment, consenting, conduct of study visits, collection of data, and maintenance of GCP throughout the original 2CARE study. All other participants listed (RN, LPN, MS, MPH, BS, BA, and non-designated) served as coordinators, and were responsible for recruitment, enrollment, conduct of study visits, collection of data, maintenance of site databases, query resolution, and GCP throughout the original 2CARE study.**

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