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Interleukin-6 as a marker of Huntington's disease progression: Systematic review and meta-analysis

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ABSTRACT

Huntington's disease (HD) is a rare, inherited disorder with a broad spectrum of manifestations that vary with disease severity and progression. Although genetic testing can readily confirm the initial diagnosis of HD, markers sensitive to HD progression are needed to aid the development of individual treatment plans. The current analysis aims to identify plasma Interleukin-6 (IL-6) as a marker of disease progression in HD patients. A systematic search of PubMed and Medline from conception through October 2021 was conducted. Studies reporting plasma IL-6 levels of mutation-positive HD patients and healthy controls that met inclusion criteria were selected. The search strategy collected 303 studies, 9 of which met analysis inclusion criteria. From included studies, plasma IL-6 levels of 469 individuals with the HD mutation and 206 healthy controls were collected. Plasma IL-6 levels were meta-analytically compared between healthy controls and individuals with the confirmed HD mutation at all stages of disease and correlated to performance on standardized measures of total cognitive and motor function. Plasma IL-6 was significantly increased in HD groups compared to controls ($g = 0.73$, 95% CI = 0.31,1.16, $P < 0.01$) and increased significantly throughout most stages of disease progression, notably between pre-manifest and manifest ($g = 0.31$, 95% CI = 0.04,0.59, $P < 0.05$) and early and moderate HD stages ($g = 0.52$, 95% CI = 0.18,0.86, $P < 0.01$). Significant correlations between plasma IL-6 levels and HD symptomatic progression were identified, with increased cytokine levels associated with more severe motor impairments ($r = 0.179$, 95% CI = 0.0479,0.304, $P = 0.008$) and more extreme disabilities in activities of daily living and/or work tasks ($r = -0.229$, 95% CI = −0.334, −0.119, $P < 0.001$). Conclusively, plasma IL-6 levels correlate with disease and motor symptom progression and may act as a viable marker for clinical use. Analysis is limited by small study numbers and highlights the need for future work to identify definitive ranges or rates of change of plasma IL-6 levels that correlate to progressive HD disease states.

1. Introduction

Huntington's disease (HD) is a progressive neurodegenerative disorder with a prevalence of 2.71 per 100,000 people (Pringsheim et al., 2012). HD is characterized by neuronal degeneration in the basal ganglia and cerebral cortex, which underlies the disorder's motor, cognitive and psychiatric manifestations. Other less well-known, but common symptoms of HD include weight loss, autonomic dysfunction and sleep and circadian rhythm disorders (Roos, 2010). In most cases, HD is officially diagnosed with the onset of motor symptoms, but many individuals develop cognitive and psychiatric manifestations years before motor symptoms begin. Following diagnosis of HD, available therapies can help manage symptoms, but do not alter the course of disease, resulting in death of affected individuals within 17–20 years (Silajdžić and Björkqvist, 2018).

HD is of genetic origin, where affected individuals carry polyglutamine repeats in the HTT gene encoding huntingtin. Wild-type alleles in the general population contain up to 35 polyglutamine repeats, whereas patients with HD carry repeat lengths of ≥36 (Rubinsztein et al., 1996). The lengths of these polyglutamine repeats serve as genetic markers for HD, allowing predictive genetic testing to identify individuals at risk for HD before the onset of symptoms. However, genetic testing in individuals with expansions of 35–39 polyglutamine repeats is not able to predict disease penetrance. Furthermore, these tests are not predictive of

Abbreviations: UHDRS, Unified Huntington's Disease Rating Scale.

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HD progression, resulting in significant demand for markers that can accurately reflect disease status to increase diagnostic and therapeutic interventions for HD patients.

Other current markers of HD progression are categorized into clinical, imaging and biochemical measures. Clinical biomarkers for HD primarily rely on the Unified Huntington's Disease Rating Scale (UHDRS), which assesses HD patients based on motor function, cognitive function, behavioral abnormalities, and functional capacity ("Unified Huntington's disease rating scale: Reliability and consistency," 1996). However, this clinical assessment lacks the sensitivity to detect subtle symptomatic changes in premanifest HD patients, and is subject to the floor effect in individuals with advanced HD (Youssov et al., 2013). Moreover, UHDRS scores may be confounded by the retest effect. Due to these limitations, measures of clinical outcomes are typically used together with brain imaging tests to diagnose and monitor the progression of HD.

Brain imaging techniques, including MRI and PET scans, have shown promise for assessing HD progression. In particular, these techniques have detected changes in HD brain structure and function that correlate with HD severity and motor dysfunction (Hobbs et al., 2010; Politis et al., 2011). Thus, there is significant diagnostic utility of imaging markers for HD; however, these methods are unable to provide a direct pathological measure of disease (Killoran, 2016).

Biochemical markers of HD progression provide a direct chemical reflection of brain injury. Thus, when used with genetic, clinical and imaging markers, biochemical markers can provide a more holistic and direct understanding of disease pathogenesis, and lead to the development of disease modifying and personalized treatments for patients. Among the most promising biochemical markers for HD progression are markers of the immune system. Studies have proposed that clusterin, Interleukin (IL)-4, IL-6, IL-8, IL-10 and TNF- α are upregulated in patients with HD and correlate with disease progression (Björkqvist et al., 2008; Wild et al., 2008). Therefore, immune system markers for HD may offer new diagnostic and therapeutic avenues for distinguishing between HD stages, and monitoring disease progression in affected patients.

In particular, IL-6, a cytokine associated with inflammatory responses in the central nervous system, has been of interest in HD pathogenesis. The mechanism of IL-6 upregulation in HD is mediated by mutant HTT (mHTT), which causes translocation of NFkB to the nucleus and subsequent transcription of IL-6 target genes (Träger et al., 2014). This upregulation of IL-6 can be detected more than a decade before the onset of HD symptoms and has been reported to be the earliest marker of immune activation in HD (Björkqvist et al., 2008). However, the limited studies that investigate IL-6 in HD have demonstrated inconsistencies in the directions of effect and levels of significance of IL-6 levels between HD and non-HD patients (Björkqvist et al., 2008; Szafran et al., 2018). Thus, this present systematic review and meta-analysis, which is the first of its kind, aims to identify whether levels of IL-6 in HD patients differ from healthy controls and throughout disease progression to the extent that IL-6 may be used as a marker to track disease progression. We further aim to determine if plasma IL-6 levels correlate with symptomatic progression of HD as determined by the UHDRS. This study can implicate potential therapeutic targets for HD, and aid in the development of holistic diagnostic measures for HD progression.

2. Methods

2.1. Publication search

The search for studies reporting plasma IL-6 levels in Huntington's disease was conducted in October 2021. Search strategies were developed in consultation with a research librarian. Searches were conducted using MedLine and PubMed and search terms for both databases were as follows: (1) Interleukin-6 AND Huntington, (2) Interleukin 6 AND Huntington, (3) IL-6 AND Huntington, (4) IL6 AND Huntington, (5) IL 6 AND Huntington, (6) Interleukin AND Huntington, and (7) Cytokine AND Huntington. Studies were limited to those published in the English language and studies involving humans, and inclusive of all studies published up to October 2021.

2.2. Publication Selection

Studies were initially screened based on titles and abstracts independently by one author (MM). Subsequently full-text review of relevant publications was conducted independently by two authors (MM and SE) to identify studies eligible for meta-analysis. Studies were considered eligible for analysis if they met the following criteria: (1) reported quantitative measures of plasma IL-6 in individuals with the HD mutation and in healthy controls, (2) reported original data; reviews were excluded, and (3) were not case reports due to low sample size.

2.3. Data extraction

Data was extracted from all included studies independently by MM and organized into a comprehensive spreadsheet which was independently checked by SE. Extracted data included sample size, sample sex, average sample age in years, type of controls used, mean IL-6 plasma measurements of HD mutation-positive individuals and controls along with corresponding SD or SEM, status of HD progression, and correlation coefficients between plasma IL-6 levels and UHDRS scores indicating total function capacity and total motor scores. When not reported, data was retrieved by MM through contacting corresponding authors via email.

2.4. Statistical analysis

Using Revman5.4 software, a random effect model meta-analysis was performed to assess differences in plasma IL-6 levels between individuals with the HD mutation and healthy controls, and between HD mutation-positive individuals at different stages of disease progression. Within-group IL-6 mean plasma levels (pg/mL) and standard deviations (SD) of healthy controls and HD mutation carriers, subsequently divided into subgroups based on disease state which was considered a potential source of heterogeneity, extracted from studies included in the meta-analysis were utilized to calculate an overall effect size, as previously described (Deeks and PT Higgins, 2007) which was visualized using forest plots produced by Revman5.4. Where applicable ($n = 1$), SD was derived from standard error, and mean (SD) was derived from median (interquartile range) (Hozo et al., 2005). Revman5.4 uses Hedges' adjusted *g* as a measure of standard mean difference (S.M.D). All models were fitted with the inverse variance statistical method, with random effect analyses and standard mean difference effect measures. Effect sizes and 95% confidence intervals (95% CI) were computed for each effect estimate, and two-tailed p-values ($P < 0.05$) indicated statistical significance between groups. Between studies heterogeneity was assessed using I^2. The statistical algorithms of Revman5 have been previously described (Deeks and PT Higgins, 2007).

Correlations between plasma IL-6 levels and UHDRS (1) total functional capacity and (2) total motor scores were compared with random effect model weights in SciStat (Armitage et al., 2008). Pearson correlations (r) were derived from β coefficients (Peterson and Brown, 2005) or spearman coefficient ("On Further Methods of Determining Correlation," 1907), and two-tailed $P < 0.05$ denoted statistical significance.

Publication bias was independently qualitatively assessed by two authors (MM and SE) using funnel plots, plotting S.M.D against the S.E. of S.M.D. or the correlation coefficient against the S.E of the included studies automated by Revman5.4 and SciStat.

3. Results

3.1. Publication Selection

Database searches produced a total of 303 publications, of which 88 were duplicates. Of the 215 resulting studies, 180 were considered irrelevant and excluded from further analysis following abstract and title review, leaving 35 studies for full-text review. 4 articles of the 35 eligible studies were not retrievable, although efforts were made to contact the corresponding authors for access to the studies, leaving 31 studies for full-text review. Further, 22 studies were excluded from analysis for not reporting plasma IL-6 levels (Battaglia et al., 2011; Bouwens et al., 2016; Chhetri et al., 2002; Crotti et al., 2014; Fiszer et al., 1991; Godavarthi et al., 2009; Godinho et al., 2014; Hsiao et al., 2013; Khoshnan et al., 2017; Kuan et al., 2016; Laprairie et al., 2014; Lee et al., 2002; Lin et al., 2019; Metzler et al., 2000; Miller et al., 2017, 2016, 2015; O'Regan et al., 2020; Quinti et al., 2017; Rodrigues et al., 2016; Silvestroni et al., 2009; Simmons et al., 2018; Träger et al., 2014; von Essen et al., 2020; Widner et al., 1999; Zhang et al., 2004). A total of 9 publications met all inclusion criteria and were included in the meta-analysis (Björkqvist et al., 2008; Bouwens et al., 2017; Chang et al., 2015; Corey-Bloom et al., 2020; Dalrymple et al., 2007; Du et al., 2021; Politis et al., 2015; Sánchez-López et al., 2012; Szafran et al., 2018) (Fig. 1). Studies were grouped in each analysis based upon the studies classification of HD patients as either HD mutation-positive, pre--manifest, manifest, early manifest, or moderate manifest. The included study characteristics and correlating HD patient classification are provided in Table 1.

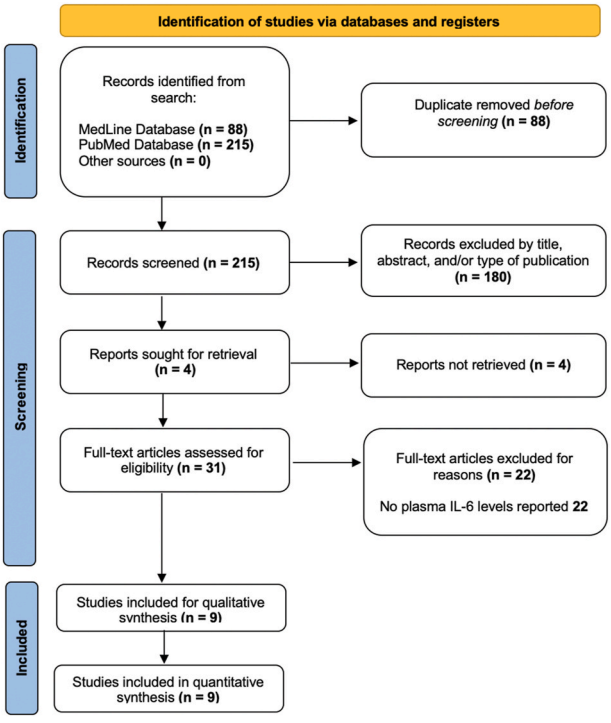

Fig. 1. Flow diagram of Publication Selection. Searches in PubMed and MedLine produced a total of 303 publications, of which 88 were duplicates. Of the resulting 215 studies, 180 were considered irrelevant and excluded from further analysis after abstract and title review, and 4 articles were not retrievable, leaving 31 studies for full-text review. Further, 22 studies were excluded from analysis for not reporting plasma IL-6 levels. The present meta-analysis includes data on 9 publications.

3.2. Study participants

The data used for the present analysis are derived from a total of 469 subjects identified to carry the HD mutation (see Table 2) and 206 healthy controls including individuals lacking the HD mutation and healthy partners of HD subjects. The average age of HD mutation carriers was reported to be 44.8 years. Of the 469 mutation carriers, 52% were identified as male and 48% as female. Classification of carriers into disease stage revealed 87 subjects to be premanifest, 180 to be considered manifest and of those 180 manifest carriers, 70 were identified to be in early stages of HD and 69 in moderate stages of HD progression.

3.3. Plasma IL-6 levels in HD groups compared to controls

Data was extracted from eight publications to determine if plasma IL-6 levels in patients carrying the HD mutation (n = 313) significantly differ from that in controls (n = 206). Patients with the HD mutation demonstrated significantly higher plasma IL-6 levels compared to control patients, with a moderate positive overall effect of 0.73 ($P = 7 \times 10^{-4}$, 95% CI = 0.31,1.16) (Fig. 2). We further conducted a separate analysis excluding a study with low-quality data (Szafran et al., 2018), where authors reported plasma IL-6 levels in patients carrying the HD mutation and controls that were considerably higher than that reported in comparable studies. Consistently, HD mutation carrying patients demonstrated significantly higher plasma IL-6 levels than controls, with a moderate overall effect of 0.74 (P = 0.001, 95% CI = 0.29,1.20) (Supplementary Fig. 1).

We further investigated if plasma IL-6 levels are markedly distinct between controls and HD groups classified by disease progression. Thus, plasma IL-6 levels were compared between controls and those classified as pre-manifest, manifest, early HD, and moderate HD (Fig. 3). Plasma IL-6 was significantly increased in patients with pre-manifest HD (n = 87) compared to controls (n = 158), with a moderately positive effect size of 0.60 ($P = 4 \times 10^{-4}$, 95% CI = 0.27,0.93). Similarly, patients with manifest HD (n = 180) had significantly higher plasma IL-6 levels than controls (n = 151), with a large effect size of 0.85 ($P < 1 \times 10^{-5}$, 95% CI = 0.62,1.08). Subsets of manifest HD patients, consisting of individuals with early (n = 70) and moderate HD (n = 69) were also compared to controls (n = 103), revealing a significant difference in plasma IL-6 levels between early HD patients and controls ($g = 0.63$, 95% CI = 0.04,1.22, $P = 0.04$) and between moderate HD patients and controls ($g = 1.23$, 95% CI = 0.89,1.56, $P < 1 \times 10^{-5}$) (results summarized in Table 3).

3.4. Plasma IL-6 levels across HD progression

To establish if plasma IL-6 levels differ across disease progression, data from 75 pre-manifest and 175 manifest HD patients were collected from four studies. Levels of plasma IL-6 were significantly increased in manifest compared to pre-manifest HD patients, with a small positive effect size of 0.31 (P = 0.03, 95% CI = 0.04,0.59) (Fig. 4).

To assess if plasma IL-6 levels increase between stages of disease progression, plasma IL-6 was compared among individuals classified as pre-manifest, early HD, and moderate HD (Fig. 5). Plasma IL-6 levels in pre-manifest (n = 50), early HD (n = 70) and moderate HD (n = 69) were extracted from two studies. Although plasma IL-6 levels did not significantly differ between pre-manifest and early HD patients ($g = -0.06$, 95% CI = −0.42,0.31, $P = 0.76$), plasma IL-6 levels were significantly increased in moderate versus pre-manifest HD patients ($g = 0.48$, 95% CI = 0.11,0.85, $P = 0.01$) and moderate versus early HD patients ($g = 0.52$, 95% CI = 0.18,0.86, $P = 0.003$); demonstrating an overall trend of increasing plasma IL-6 levels with HD progression ($g = 0.32$, 95% CI = 0.07,0.58, $P = 0.01$).

Table 1
Summary of data collected from 9 included studies. [a]

First Author (Year)	Control Type	Control (n)	Total Patients (n)				
			HD Mutation Carriers	Pre-Manifest HD	Manifest HD		
					n	Early HD	Moderate HD
Du et al. (2021)	Healthy	33	33	–	–	–	–
Corey-Bloom (2020)	Healthy	27	73	20	21	–	-
Szafran et al. (2018)	Non-HD	5	5	–	5	–	–
Bouwens et al. (2017)	–	–	124	–	–	–	–
Chang et al. (2015)	Healthy	16	20	5	15	–	–
Politis et al. (2015)	Healthy	12	12	12	–	–	–
Sánchez-López (2012)	Healthy	10	13	–	–	–	–
Björkqvist et al. (2008)	Lacking the HD mutation	69	127	34	93	47	46
Dalrymple et al. (2007)	Partners of HD patients, at-risk individuals lacking the HD mutation, and healthy	34	62	16	46	23	23

[a] Abbr.: Healthy: No history of neurological and/or psychiatric disorders or detection of HD mutation, Non-HD: Individuals not carrying the HD mutation.

Table 2
Description of HD mutation carriers included in analysis. [a]

Characteristic	No.
Total Number of HD Mutation Carriers	469
Mean Age (years)	44.8
Male:Female (%)	52:48
Premanifest	87
Manifest	180
Early HD	70
Moderate HD	69

[a] Mean age and male:female ratios are a reported estimate due to 1 paper not reporting patient demographics and 1 paper providing demographics for the entire patient population, but not individual subgroups that underwent IL-6 data collection.

3.5. Correlations between plasma IL-6 and symptomatic progression of HD

To establish the relationship between plasma IL-6 and symptomatic progression of HD, data from measures of UHDRS total functional capacity (TFC) and total motor scores (TMS) were analyzed, where greater TFC indicates higher patient functioning and greater TMS indicates more severe motor impairments. Plasma IL-6 levels in HD gene expansion carriers were inversely correlated with TFC ($r = -0.229$, 95% CI = −0.334, −0.119, $P = <0.001$) (Fig. 6 & Table 4) and positively correlated with TMS ($r = 0.179$, 95% CI = 0.0479, 0.304, $P = 0.008$) (Fig. 7 and Table 5).

3.6. Publication bias

Publication bias for the six analyses of plasma IL-6 levels in patients carrying the HD mutation compared to healthy controls, plasma IL-6 levels in individuals with HD compared to healthy controls at different stages of disease progression, plasma IL-6 levels in pre-manifest compared to manifest HD patients, plasma IL-6 levels compared across different stages of HD progression, correlation between plasma IL-6 and TFC, and correlation between plasma IL-6 and TMS was not found to be a significant factor in the present meta-analysis (Fig. 8). Symmetric scattering of the published data on either side of the respective overall effect sizes (8A-D) and correlation coefficients (8E and F) can be observed for each of the corresponding funnel plots.

4. Discussion

The aim of the current study was to identify plasma IL-6 as a marker of disease and symptomatic progression in HD patients. Analysis of data pooled from 9 studies collectively derived from 469 individuals with the HD mutation at varying stages of disease revealed that plasma IL-6 levels are significantly elevated in HD at all stages of disease progression, which became increasingly notable at each step of disease advancement. IL-6 increased significantly between most stages of disease progression, with a notable increase between pre-manifest and manifest and early and moderate disease states. Plasma IL-6 was significantly correlated with UHDRS TFC and TMS scores, where increased plasma IL-6 was found to be associated with more severe functional decline and motor impairments in HD patients. These results are consistent with previous findings of an upregulation of IL-6 in the striatum, cortex and cerebellum of post-mortem human HD tissue (Silvestroni et al., 2009).

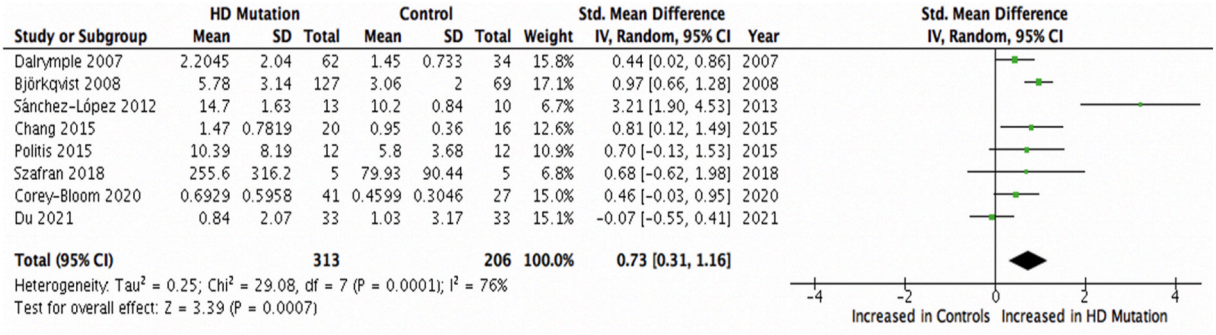

Fig. 2. Plasma IL-6 levels in HD and control patients. Forest plot of plasma IL-6 levels in patients carrying the HD mutation (n = 313) compared to controls (n = 206). Patients with the HD mutation demonstrated significantly higher plasma IL-6 levels compared to control patients ($g = 0.73$, P = 0.0007, 95% CI = 0.31,1.16).

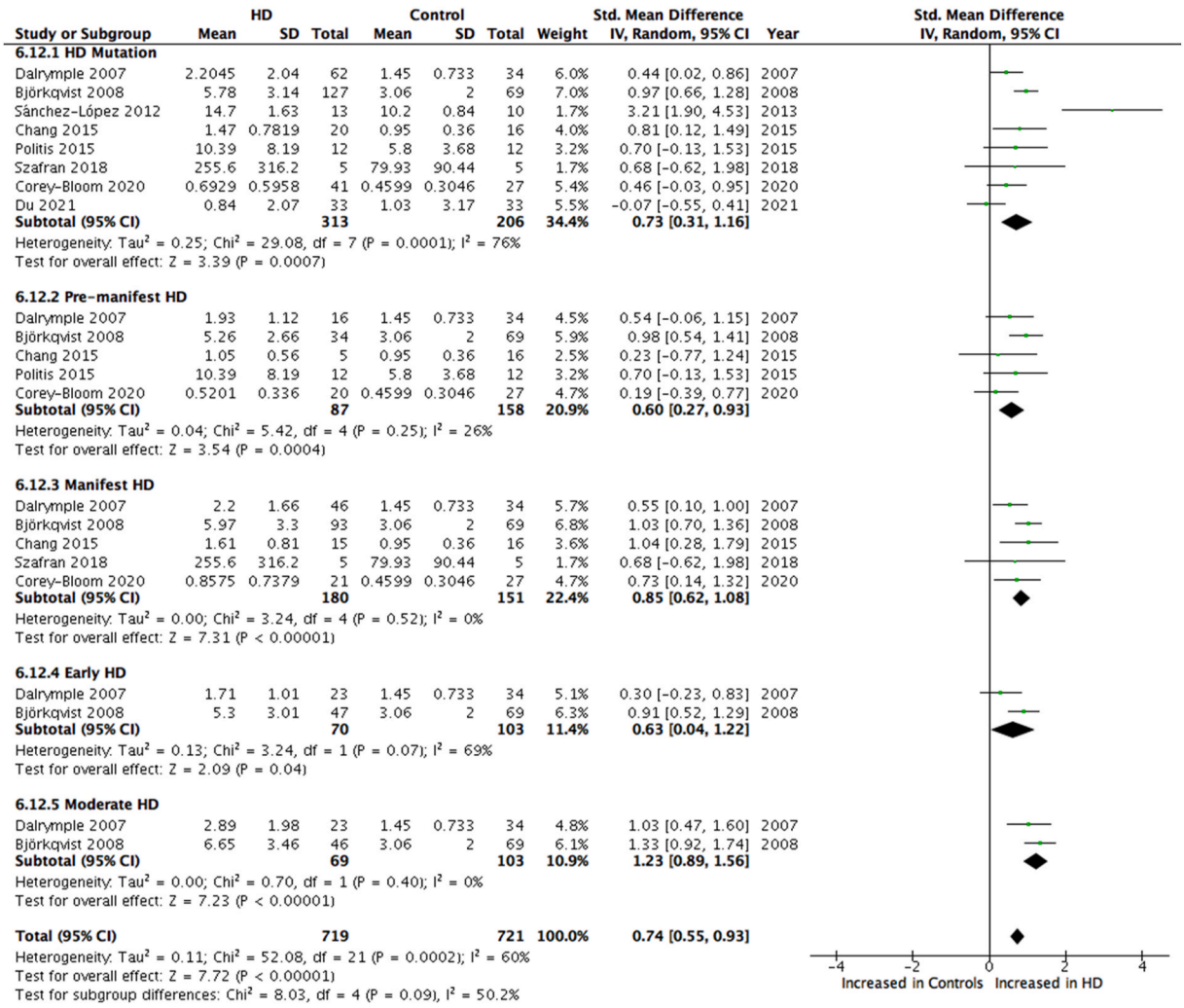

Fig. 3. Plasma IL-6 levels in individuals with HD compared to controls at all stages of disease progression. Those with the HD mutation (n = 313) present with higher levels of plasma IL-6 compared to controls (n = 206), which is prevalent in every stage of HD progression including pre-manifest (n = 87), manifest (n = 180), early HD (n = 70), and moderate HD (n = 69) with overall significant positive effect sizes.

Table 3
Effect sizes (Hedge's *g*) of differences in plasma IL-6 Levels in defined HD Groups Compared to Controls.

	Controls		
	Effect Size	**95% CI**	***P* value**
HD Mutation	0.73	0.31,1.16	7×10^{-4} **
Pre-manifest HD	0.60	0.27,0.93	4×10^{-4} **
Manifest HD	0.85	0.62,1.08	$<1 \times 10^{-5}$ **
Early HD	0.63	0.04,1.22	0.04*
Moderate HD	1.23	0.89,1.56	$<1 \times 10^{-5}$ **

*P < 0.05, **P < 0.01.

Furthermore, plasma IL-6 has been found to positively correlate with motor scores and disease severity in Parkinson's disease (Green et al., 2019).

Studies suggest that IL-6 is elevated in HD through indirect action of mHTT on cellular pathways responsible for regulating IL-6 transcription. In response to neuronal degeneration, mHTT promotes the degradation of the inhibitory IkB kinase complex via phosphorylation, leading to its dissociation from the NFkB transcription factor (Khoshnan et al., 2017; Kraft et al., 2012). The free NFkB subsequently translocates to the nucleus and binds the IL-6 promoter to activate gene transcription (Libermann and Baltimore, 1990) (Fig. 9). This excessive NFkB pathway activation has been previously observed in HD patients and mouse models, and has been linked to deleterious neuroinflammation as well as motor and cognitive deficits in animal HD models suggesting an active role of IL-6 in disease presentation (Khoshnan et al., 2004; Liu et al., 2018).

Aggregates of mHTT are associated with blood brain barrier (BBB) impairments in the striatum of HD patients and mice (Drouin-Ouellet et al., 2015). This BBB disruption may in part be mediated by chronically elevated levels of IL-6, which has been previously shown to alter the regulation of genes involved in BBB permeability, including that of cellular tight junctions, focal adherens complexes, and cell adhesion molecules (Simon et al., 2021). Alterations in the BBB can facilitate the entry of neurotoxins into the brain and disrupt the delicate ion-water balance of the neuronal environment, resulting in neuronal damage and dysfunction observed in HD (Daneman and Prat, 2015; Sweeney et al., 2018). Interestingly, impaired BBB permeability has been demonstrated to correlate with HD onset, and is more significantly altered in patients and mice with severe HD symptoms with potential contributions to worsening cognitive dysfunction (Drouin-Ouellet et al., 2015; Wertz et al., 2020; Zhao et al., 2015). Consequently, this mechanism of IL-6 mediated BBB dysfunction may partially explain the presently observed correlations between higher levels of plasma IL-6 and more severe functional decline and motor impairments in HD patients.

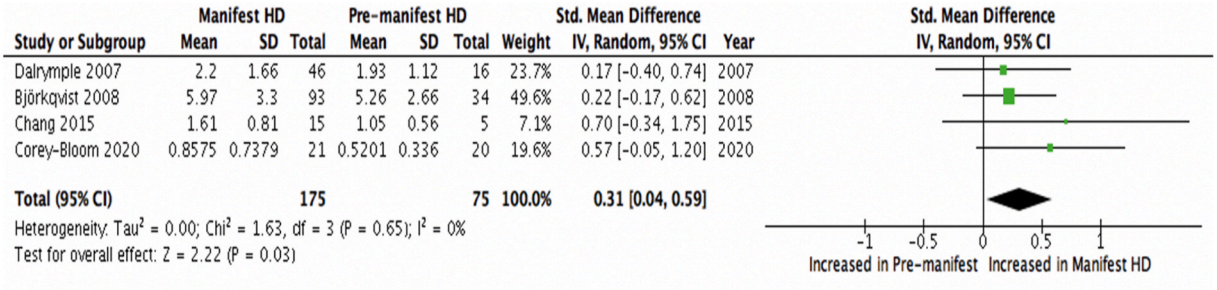

Fig. 4. Plasma IL-6 levels in Manifest and Pre-manifest HD Patients. Forest plot comparing plasma IL-6 levels in pre-manifest (n = 75) and manifest (n = 175) HD patients. Levels of plasma IL-6 were significantly increased in manifest compared to pre-manifest HD patients, with a small positive effect size of 0.31 (P = 0.03, 95% CI = 0.04,0.59).

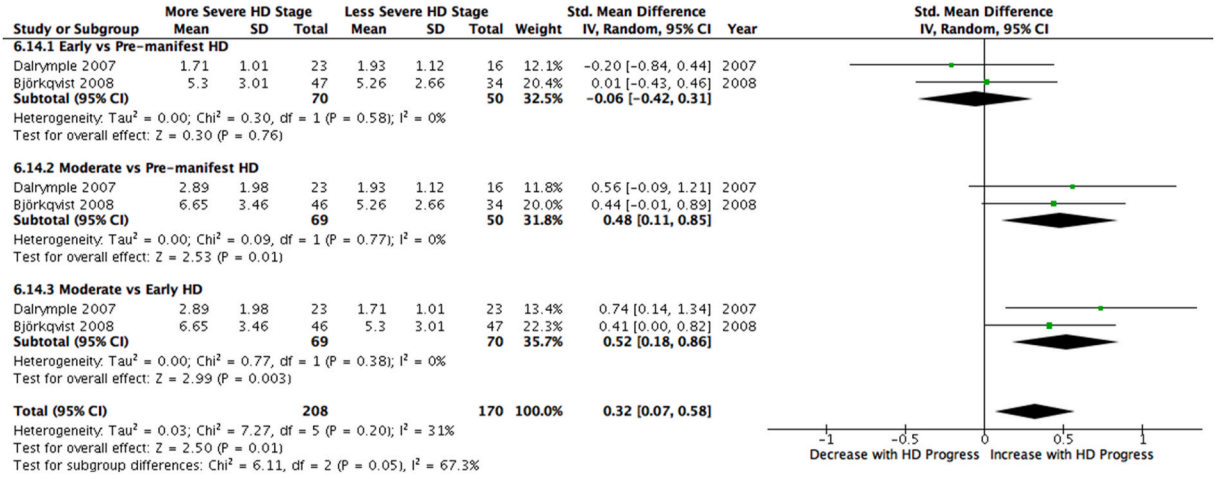

Fig. 5. Plasma IL-6 levels compared across various stages of disease progression. Plasma IL-6 levels did not significantly differ between pre-manifest (n = 50) and early HD patients (n = 70) ($g = -0.06$, 95% CI = −0.42,0.31, P = 0.76) but do significantly increase in moderate HD patients (n = 69) compared to pre-manifest HD patients (n = 50) ($g = 0.48$, 95% CI = 0.11,0.85, P = 0.01) and early HD (n = 70) ($g = 0.52$, 95% CI = 0.18,0.86, P = 0.003).

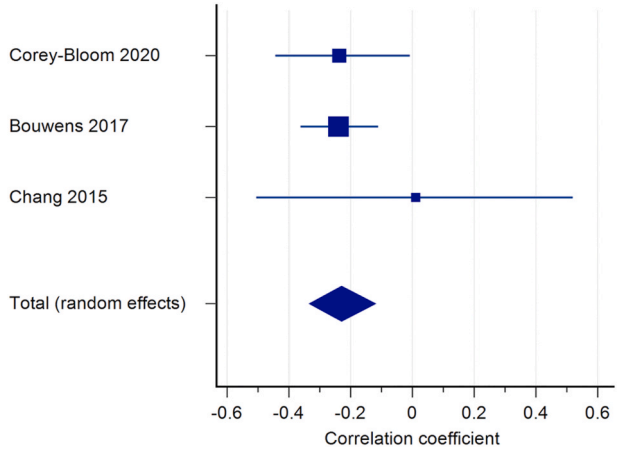

Fig. 6. Correlation between Plasma IL-6 and Total Functional Capacity Scores. Forest plot of correlation coefficients between plasma IL-6 levels and UHDRS total functional capacity scores. Plasma IL-6 levels in HD gene expansion carriers were inversely correlated with total functional capacity scores (r = −0.229, 95% CI = −0.334, −0.119, P= <0.001).

In addition to motor symptoms, HD is associated with psychiatric symptoms which can significantly impact daily functioning and quality of life. Psychiatric symptoms, which are noted to include depression, anxiety, irritability, psychosis, hostility, and obsessive-compulsive behaviour, manifest early on in expansion-positive individuals and may predate clinical diagnosis (Duff et al., 2007; Epping et al., 2016). Longitudinal study suggests that psychiatric symptoms worsen with disease progression (Epping et al., 2016). Correlational data looking at cytokine levels and psychiatric symptoms of HD are limited and thus could not be included in the present analysis. While animal studies suggest a potential correlation between plasma IL-6 levels and both anxiety and irritability scores in HD models (Podlacha et al., 2022; Raper et al., 2016), human data does not demonstrate the same relationship, with no correlation found between any inflammatory cytokine and HD-associated neuropsychiatric symptoms (Bouwens et al., 2016). Interestingly, recent data imply that the propensity for self-reported depression and psychosis in HD individuals is driven by the same genetic predispositions as viewed in the general population (Ellis et al., 2020); while other reports suggests symptoms of depression and change in affect occur in response to clinical diagnosis and are independent of HD disease mechanisms (Epping and Paulsen, 2011). Further, while IL-6 is found to be elevated in those reporting depression, plasma IL-6 is most significantly elevated in those with a diagnosed depressive disorders compared to those experiencing depression as a symptom of a disorder (Hiles et al., 2012). Thus, based on the present literature if elevated plasma IL-6 levels are correlated with psychological symptoms of HD, it may be more likely IL-6 levels are correlated to anxiety and irritability rather than depression, as is observed in animal models (Podlacha et al., 2022; Raper et al., 2016), and further may contribute to the development of anxiety long-term (Niraula et al., 2019), however further research is required.

Since the current analysis finds plasma IL-6 correlates with HD severity and previous reports suggest IL-6 contributes to neurotoxicity in

Table 4
Correlations (r) between plasma IL-6 and total functional capacity scores.

Total Functional Capacity						
Study	N	Correlation coefficient (r)	95% CI	z	P	Weight (%)
Corey-Bloom (2020)	73	−0.237	−0.443, −0.00733			37.57
Bouwens et al., 2017	216	−0.240	−0.362, −0.110			72.20
Chang et al., 2015	15	0.010	−0.505, 0.520			4.07
Total	304	−0.229	−0.334, −0.119	−4.013	<0.001	100.00

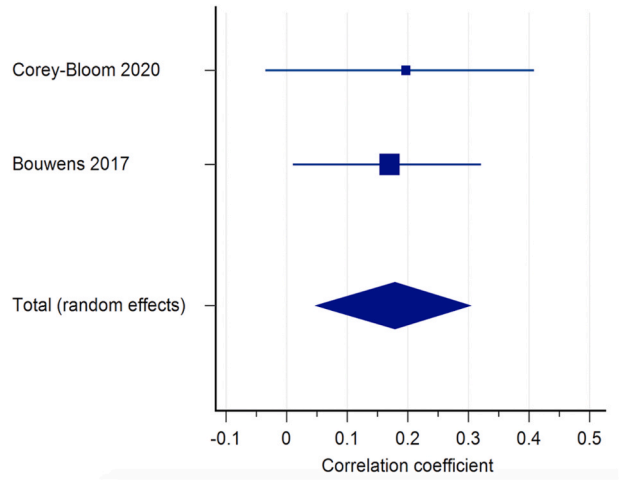

Fig. 7. Correlation between Plasma IL-6 and Total Motor Scores. Forest plot of correlation coefficients between plasma IL-6 levels and UHDRS total motor scores. Plasma IL-6 levels in HD gene expansion carriers were positively correlated with total motor scores (r = 0.179, 95% CI = 0.0479, 0.304, P = 0.008).

Table 5
Correlations (r) between plasma IL-6 and total motor scores.

Total Motor Score						
Study	N	Correlation coefficient (r)	95% CI	z	P	Weight (%)
Corey-Bloom (2020)	73	0.197	−0.0346, 0.409			32.11
Bouwens et al., 2017	151	0.170	0.0106, 0.321			67.89
Total	224	0.179	0.0479, 0.304	2.667	0.008	100.00

HD (Khoshnan et al., 2004), it would be reasonable to consider IL-6 as not only a clinical marker of disease progression but also as a potential therapeutic target for HD. In particular, the use of the IL-6 inhibitor, Tocilizumab, has been previously investigated in Alzheimer's disease, where rat models exhibited significant improvements in learning and spatial memory functions (Elcioğlu et al., 2016). However, to the contrary, a study of HD mice lacking IL-6 demonstrated significantly exacerbated disease-associated behavioural phenotypes compared to HD mice able to express IL-6 (Wertz et al., 2020). These results suggest that IL-6 may have an early protective role in HD but given the impact of chronic IL-6 activity on the BBB and neuronal viability, prolonged IL-6 activity may be detrimental in later stages of disease. This phenomenon may correspond to the initial insignificant difference in IL-6 levels between pre-manifest and early HD patients, where it was found that although pre-manifest and early HD subjects had higher levels of plasma IL-6 than controls, no difference was found between patients at these stages of disease, potentially marking a time where IL-6 production and activity is controlled and acting in a protective role. However, as HD progresses, IL-6 levels significantly rise in patients, potentially reaching chronically elevated levels detrimental to neural function, corresponding to more severe illness and pronounced motor and functional symptoms. Thus, beyond acting as a clinical marker, IL-6 may also be a viable target for HD treatment in later stages of disease, but this remains to be explored.

Whether or not IL-6 is an active player in HD pathology, IL-6 does appear to be a promising clinical marker for HD that can inform disease presence and progression. Importantly, IL-6 markers reflect one of the most critical pathophysiological mechanisms of HD by measuring the extent of BBB disruption (Uchida et al., 2017). This measure of disease can help evaluate personalized therapeutic interventions for HD and identify specific patient populations that may benefit from targeted therapies. IL-6 markers also provide a more objective and quantitative measurement of HD severity compared to current clinically based outcomes and are a cheaper alternative to imaging techniques.

It should be noted that IL-6 is not a specific marker for HD, and has been implicated in Alzheimer's disease (Angelopoulos et al., 2008) and amyotrophic lateral sclerosis (ALS) among others (Wosiski-Kuhn et al., 2021), and thus should be considered as an adjunctive measure of disease that may inform decision to employ more expensive and/or invasive means of monitoring disease trajectory. Thus, current hope lies in pathophysiologically-relevant IL-6 markers, in combination with existing biomarkers for HD, to improve diagnostics and personalized therapeutics for patients. An existing pool of biological and behavioural markers have been associated with HD severity and collectively provide an indication of motor, cognitive and structural deficits in HD patients. These diverse markers, which in combination with levels of plasma IL-6 as indicated by the present analysis, may be utilized to define a readily measurable pattern of physiological and behavioural irregularities that may inform disease and symptom progression (Fig. 10). Plasma Neurofilament light chain, Interlukein-8, TNF-α, and salivary brain-derived neurotrophic factor (BDNF) and total huntingtin protein (tHtt) have established correlations to HD progression and may be easily assessed in HD patients through sampling of the plasma and saliva (Björkqvist et al., 2008; Byrne et al., 2017; Corey-Bloom et al., 2018; Gutierrez et al., 2020). Additionally, association between some of these biomarkers and IL-6 have been identified. TNF-α has been shown to induce IL-6 and IL-8 release in the central nervous system, and BDNF and plasma IL-6 levels have been negatively correlated in a study of cancer-related cognitive impairment (Ehrlich et al., 1998; Tanabe et al., 2010; Yap et al., 2021). As a result, the combination of these interrelated biomarkers may provide more extensive insight into the mechanism and stage of neurodegeneration in the brain to improve diagnostic and treatment accuracy in HD. Additionally, the measurement of biological markers of disease may be supplemented with structural and behavioural markers of disease progression, notably structural loss identified through imaging techniques (Russell et al., 2014; Tabrizi et al., 2013) and performance in the symbol digit modality test, anti-saccade error rate, and digitomography which have all been established to track HD progression (Tabrizi et al., 2009, 2013). Conclusively, a combination approach utilizing the measurement of a network of biomarkers correlated to HD severity, may allow clinicians to objectively assess therapeutic efficacy and structure individualized treatment plans based on multiple quantitative measures of neurodegeneration.

The present analysis supports the use of plasma IL-6 as a marker in

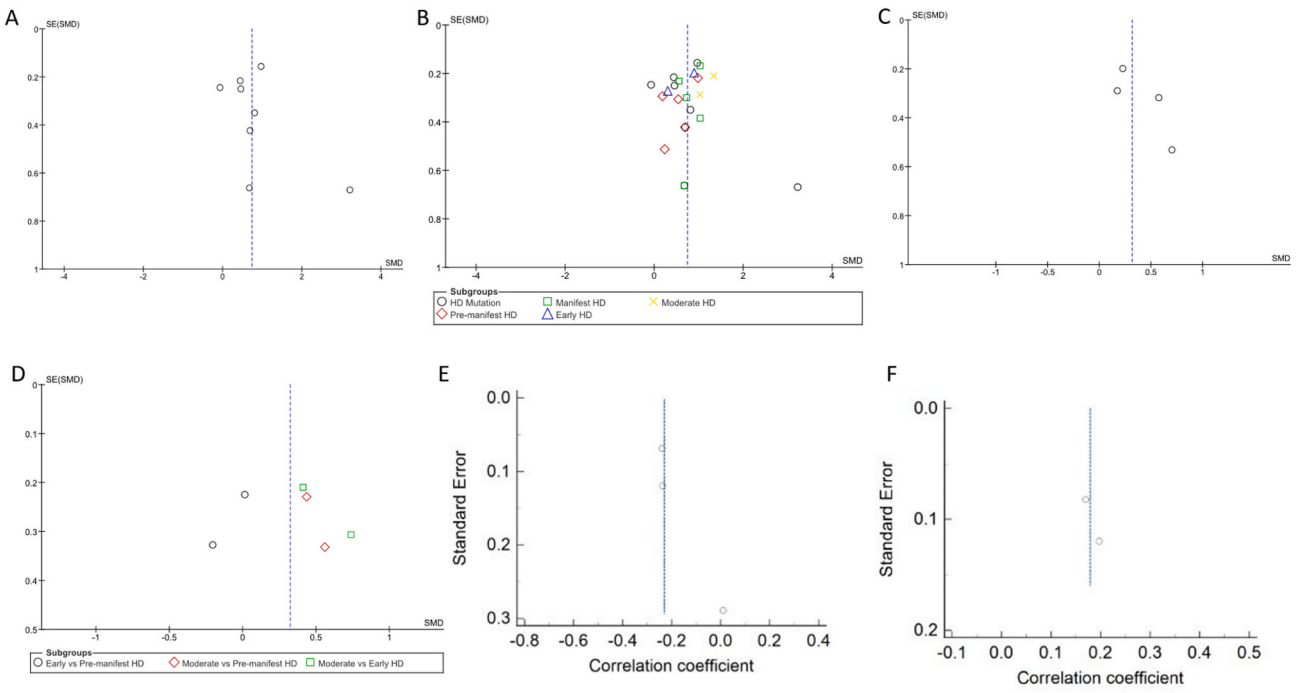

Fig. 8. Funnel Plots. (A) Funnel plot of studies reporting plasma IL-6 in all HD mutant-positive patients (B) Funnel plot of studies reporting plasma IL-6 in HD patients at different stages of disease compared to healthy controls (C) Funnel plot of studies reporting plasma IL-6 in manifest vs pre-manifest HD patients (D) Funnel plot of studies reporting plasma IL-6 across different stages of HD progression (E) Funnel plot of studies reporting correlation coefficients of plasma IL-6 and total functional capacity (F) Funnel plot of studies reporting correlation coefficients of plasma IL-6 and total motor scores.

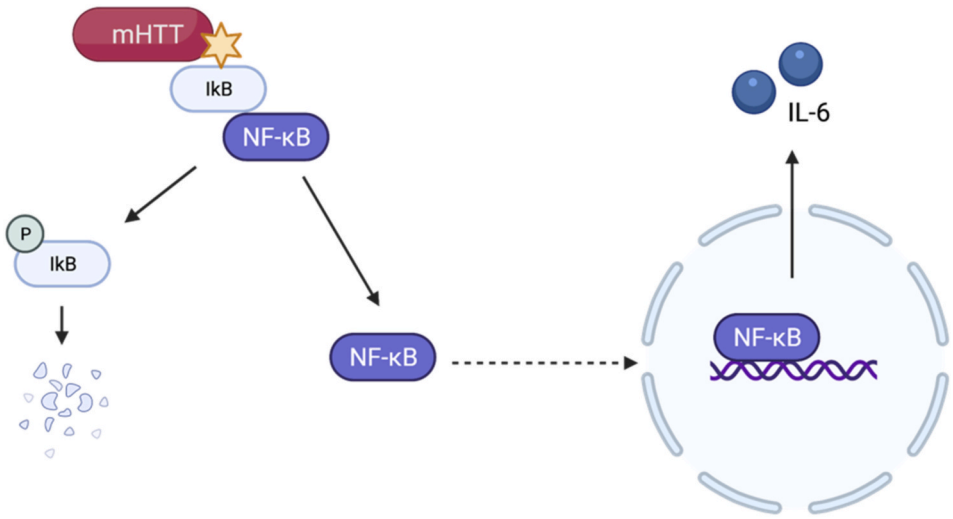

Fig. 9. Mechanism of IL-6 production in HD. In response to neuronal degeneration, mHTT promotes the degradation of the inhibitory IkB kinase complex via phosphorylation, leading to its dissociation from the NFkB transcription factor. The free NFkB can subsequently translocate to the nucleus and bind the IL-6 promoter to activate gene transcription. (Created with BioRender.com).

HD, with emphasis on its correlation with disease and symptom progression. It should be noted that this analysis was limited by the relatively small number of studies that met inclusion criteria. However, the minimum requirement to conduct a meta-analysis is 2 studies so long as the studies can reasonably be considered similar in nature (Ryan, 2016). Given our strict inclusion criteria and the transparent reporting of heterogeneity for each analysis we do not think the number of studies the analysis is based on invalidates the present conclusions. Rather, we hope that the present analysis leads to further works dedicated to growing and diversifying the current understanding of changes in plasma cytokines levels in HD patients, including IL-6, and specifically how inflammatory cytokine profiles change with disease progression. Future work should look to quantitatively define ranges of plasma IL-6 levels across states of disease progression or quantify the rate of change in plasma IL-6 levels as individuals progress through disease states. Such information could be directly applied to clinical practice and provide the framework to estimate timeframes for disease and symptom progression based on plasma IL-6. Unfortunately, the nature of pooling heterogenous data derived from different studies does not allow for such conclusions in the current analysis. Another potential limitation of the present analysis is the inclusion of HD partners (Dalrymple et al., 2007) and ambiguous inclusion criteria which may also result in the inclusion of HD partners

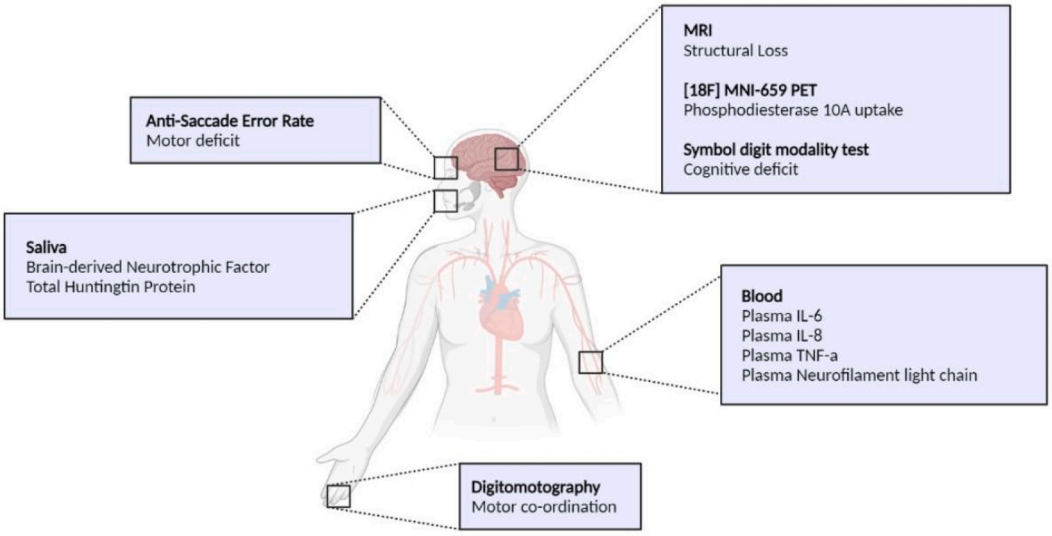

Fig. 10. Biological and behavioural markers of HD Severity. An extensive range of biological and behavioural markers of HD progression have been identified and can be assessed through sampling the blood and saliva, brain imaging, and behavioural tests which may be used in combination to track disease in addition to plasma IL-6. (Created with Biorender.com).

(Björkqvist et al., 2008; Szafran et al., 2018) in control groups who are not confirmed to be free of psychiatric or neurological symptoms. As discussed above, plasma IL-6 levels may correlate to symptoms of depression, anxiety, and irritability (Hiles et al., 2012; Podlacha et al., 2022; Raper et al., 2016). Care-partners of HD patients are found to experience greater levels of depression and anxiety compared to controls as a result of living with and caring for an individual with a progressive neurological disorder (Exuzides et al., 2022). While this should not impact comparison across those at different stages of HD progression, it may skew results comparing plasma IL-6 levels of those with HD and those without if care-partners are included as controls. However, if control data is derived from care-partners, reported control IL-6 levels may be higher than expected of the general population and thus any significant difference in the present analysis between HD individuals and controls is thus underreported. Therefore, it is not expected that the inclusion of care-partners in control data significantly impacts the conclusions of the present analysis, but should be taken into consideration when reviewing the data. Our analysis also demonstrates that plasma IL-6 increases with HD progression, particularly from pre-manifest to moderate HD, and early HD to moderate HD stages. Given that prior studies have noted changes in UHDRS scores with disease progression (Siesling et al., 1998), we cannot fully ascertain whether the correlations we observed between plasma IL-6 and TFC and TMS are true, or independent artifacts of disease progression; future studies are required to validate this finding. Further, few studies take into consideration potential biological sex differences, which unfortunately due to limited reporting this study could not include as a variable in sub-group analysis to explain any observed heterogeneity of effect sizes. There remains the potential that within HD, disease progression (Zielonka et al., 2013) and plasma IL-6 levels (Bruzelius et al., 2019; O'Brien et al., 2007) differ based on sex. Future research should focus on identifying potential sex-based differences in HD manifestations, and the molecular mechanisms that lead to these alterations, including cytokine production. Additionally, as discussed, future studies should also explore IL-6 as a therapeutic target for HD in later stages of disease. These studies can complement our current findings to aid in the development of improved diagnostic measures and individualized treatments to ameliorate the day-to-day complications afflicting those with Huntington's disease.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2023.100635.

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