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HIV-Related Stigma Affects Cognition in Older Men Living with HIV

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Declaration of Interests

The authors have no conflicts of interest to disclose.

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Brain health consequences of HIV-related stigma

Abstract

Background

Stigma remains a reality for many people living with HIV. Stigma bears on mental health, but we hypothesized that it might also affect cognition, in turn affecting function.

Methods

We estimated the impact of HIV-related stigma on brain health and everyday functioning among 512 older Caucasian men living with HIV in Canada, using the International Classification of Functioning, Disability and Health as a comprehensive framework to integrate biopsychosocial perspectives. Experience of HIV-related stigma, as indicated by a single self-report item, was related to cognitive test performance, cognitive symptoms and mood. Structural equation modelling was used to estimate the relationships between these variables.

Findings

A comprehensive structural equation model was built including personal, environmental, biological factors, and measures of mental and cognitive health, activity limitations, and participation restrictions. HIV-related stigma contributed to lower cognitive test performance and worse mental health. These in turn affected real world function. The paths from stigma to cognition and mood had distinct downstream effects on physical, cognitive and meaningful activities.

Interpretation

This provides evidence that HIV-related stigma is a threat to cognitive as well as mental health, with a negative impact on everyday function in men aging with HIV. This argues for direct links between the psychosocial and biological impacts of HIV at the level of the brain. Stigma reduction may be a novel route to addressing cognitive impairment in this population.

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Keywords: HIV-associated neurocognitive disorders; neuroscience; brain; mental health; structural equation modeling

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Introduction

Advances in anti-retroviral treatment accessibility and effectiveness mean that HIV infection can now be considered a chronic disease. This brings new priorities for clinical care, including quality of life (QOL) and everyday function. Optimizing these outcomes for people aging with HIV infection requires an understanding of both biological and psychosocial contributors[1–3].

Even with good viral suppression, cognitive impairment is reported in 30-50% of people with HIV in research cohorts, with prevalence increasing with age. This impairment is usually mild, but still can have consequences in everyday life[3–5]. The underlying causes are not fully understood and the potential for reversibility is unknown. Current research has focused on biological factors, such as viral, cerebrovascular, and accelerated aging effects[3,5]. However, psychosocial contributors are also likely. Mental health problems are common in this population and may share causal pathways or interact with cognitive impairment. Furthermore, although brain health indicators are typically conceived of as characteristics of the affected individual, the environment in which people live with HIV likely contributes to both cognitive performance and mental health[6].

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Among potentially relevant factors, stigma stands out. Operationalized as negative attitudes towards a person held by an individual, a group, or society at large, the experience of stigma remains an important aspect of living with HIV[7]. In a recent systematic review of stigma in the cART era, over 50% of people with HIV reported experiencing stigma[8]. Different facets of stigma are recognized, such as experienced, anticipated and internalized stigma[9]. Although these are important to understand for stigma reduction purposes, they tend to show at least moderate inter-correlation[10]. In general, stigma acts as a barrier to full participation of the individual in personal, family, and societal roles[11]. In a recent study of QOL in a large sample of older people living in Canada with HIV infection[12], stigma was spontaneously reported as a priority area affecting QOL[13]. That study also highlighted the special importance of stigma in HIV, as it was not reported on the same open-ended QOL questionnaire by people living with other serious chronic conditions, including stroke, multiple sclerosis, and cancer. The importance of stigma to QOL is well-recognized in HIV research and care: Stigma is included as a domain in the World Health Organization's HIV-specific measure of QOL (WHOQOL-HIV)[14].

The relationship of stigma and mental health in people living with HIV has been extensively studied, as summarized in recent meta-analyses and systematic reviews[1,8,15]. However, the impact of stigma on other aspects of brain function, notably cognition, has not been addressed. There are several potential mechanisms by which stigma could affect cognition. First, it could act through its impact on mental health, given that depression and anxiety may themselves influence cognition. Second, by affecting social experience, stigma might affect brain structure and function directly. Variation in social network size in healthy older adults has been associated with variation in the structure of specific brain regions and their inter-connections[16], replicating findings in non-human primates assigned to social groups of different sizes[17]. This

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work argues that the social environment can change the brain structure. Third, as a chronic stressor, stigma may also affect cognition through other neurobiological mechanisms, with effects on the hypothalamic-pituitary axis[18,19], neuroinflammation[20,21], and cerebrovascular risk[22]. Finally, cognitive performance can be affected by internalized stigma: that is, people respond to internalized negative stereotype expectations, performing worse in a testing situation than others not belonging to a stigmatized group[23].

Here, we propose that HIV-related stigma has negative effects on both mental health and cognition, and that these effects will, in turn influence everyday functioning in people with HIV. Potentially complex relationships between stigma, cognition, and mental health have been suggested[21], but this view has yet to be tested empirically. Given this complexity, an understanding of the paths by which these variables affect real-world function is needed to guide work aiming to preserve or improve brain health in HIV. Here, we apply structural equation modeling (SEM) and a well-established conceptual framework, the World Health Organization's biopsychosocial model from the International Classification of Functioning, Disability and Health (ICF)[11] to systematically address this complexity in a large, well-characterized sample drawn from the Positive Brain Health Now (BHN) cohort. This longitudinal cohort study of aging with HIV aims to characterize the contributors to, and consequences of cognitive and mental health difficulties in older individuals on antiretroviral treatment, with well-controlled infection. The specific objective of the present analysis was to identify direct and indirect relationships among stigma, cognition, anxiety, depression and everyday function in older Caucasian men living with HIV in Canada.

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Methods

Source of Data

The data for this analysis came from the BHN cohort, a prospective study involving 856 older persons living with HIV recruited between 2014 and 2016 from five clinics in Canada. The study protocol has been published[12]. The project was approved by the Research Ethics Boards (REB) of all participating institutions and all participants provided written informed consent.

Participants

Participation in the BHN cohort was restricted to people age ≥35 years, HIV+ for at least 1 year, on stable combined antiretroviral treatment for at least 6 months. Exclusion criteria included dementia of stage 3 or worse on the Memorial Sloan-Kettering dementia severity scale[24], as judged by the treating physician (i.e. a severity that precludes informed consent), a non-HIV-related neurological disorder likely to affect cognition, active CNS opportunistic infection, psychotic disorder, substance dependence or abuse within the past 12 months or life expectancy of < 3 years as judged by the treating physician (see[12] for details).

Of the 856 subjects in the BHN cohort, only data from the 512 Caucasian men were analysed here to avoid the confounding effects of gender and race which are known to also influence stigma in people living with HIV[15,25]. Caucasian men were by far the largest demographic sub-group represented in this cohort, reflecting the demographics of the recruitment sources. Sample sizes of other racial sub-groups or women in this dataset were too small to support the SEM approach.

Study participants provided written informed consent, and the protocol was approved by the institutional review boards of all participating centres. This project received funding from the

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Canadian Institutes of Health Research. The funding agency had no role in the design, data collection, analysis, or interpretation of the study, nor in the writing of the report or decision to submit the paper for publication.

Measurement

The measurement framework for this study was the ICF. This provided an *a priori* model, avoiding the pitfalls arising from analyzing high dimensional correlated data without specific hypotheses concerning the paths among variables. This model links physiological and structural variables leading to symptoms or impairments, in turn affecting activities and participation common in everyday function, all of which relate to health perception and quality of life. We focused on the paths between stigma, cognitive, and mental health variables, but did so within this comprehensive model, systematically assessing the variables that influence stigma, tracing the downstream, real world impact of stigma on brain health, and contextualizing stigma effects on real world function relative to other paths in the model.

The data were collected from direct measurement, self-report questionnaires, and chart review. Table 1 presents the structure of the measurement model and an overview of the measures, as well as the demographic, clinical and environmental factors included. All self-report measures are well-known instruments with strong psychometric properties[26–28]. Cognitive performance was directly measured with a short battery of computerized tests of processing speed, attention, memory and executive function (B-CAM)[29]. This battery was developed to measure cognitive ability in older people with HIV. Although multiple domains are assessed, empirical work guided by item-response theory has established that these tests reflect a single underlying latent variable in HIV. Rasch analysis allows a single score measuring overall cognitive ability to be assigned[30]. Depression and anxiety symptoms were elicited with the

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Mental Health Index[31] and the Hospital Anxiety and Depression Scale[32]. Self-reported cognitive function limitations were ascertained with the 20-item Perceived Deficits Questionnaire[33]. HIV-related experienced stigma was assessed using a single item from the Beliefs Domain of the WHOQOL-HIV BREF questionnaire "To what extent are you bothered by people blaming you for your HIV status?" which has 5 response options ("not at all" to "an extreme amount")[34]. Details of all self-report measures, including example items are provided as Supplementary Material (Table S1,http://links.lww.com/QAI/B234).

Statistical Methods

SEM was used to test the theoretical model against the observed data. SEM encompasses factor analysis, path analysis, and regression[35]. Measured and latent variables (i.e. variables for which no single measure can reflect the construct adequately) were included in the structural model; pathways between the variables were used to calculate direct effects. Single imputation was done to address potential bias arising from incomplete data using SAS 9.3 proc mi. Factor analysis was used to define anxiety and depression latent variables, both of which drew on the Hospital Anxiety and Depression Scale (HADS) and RAND-36 Mental Health Index[12].

The SEM model for HIV-related stigma were developed sequentially, with the ICF model providing the theoretical framework. Generally, the strategy was to allow variables within the ICF rubrics to correlate, and to apply paths across the rubrics of the ICF model (Table 1). Paths were applied from personal factors, environmental factors, and biological factors to the rubrics of impairments, activity limitations, and participation restrictions. Under the impairments rubric, we focused on HIV-related symptoms, stigma, cognition and mental health. Initially, the model only included adjacent paths between the ICF rubrics of impairments, activity limitations, and participation restrictions. Paths that were not statistically significant were removed, unless

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deemed theoretically relevant. Paths across more distant ICF rubrics were added later in model development and were retained when fit was improved. While SEM assumes multivariate normality, many variable-specific measures were not normally distributed, so robust maximum likelihood estimation was used. Model fit was determined by the Satorra-Bentler scaled χ^2 and measures of approximate fit, more informative when sample sizes are large.

Results

Table 2 presents the characteristics of the sample of 512 men (mean age 54 years, SD 8) on variables under the rubrics of the ICF model. As the imputed data were very close to the observed data, only the observed data (means and standard deviations (SD)) are provided. Mean duration of HIV infection was 17.4 years (SD 8). All participants were treated with cART. 92% had complete viral suppression at the baseline visit and 96% had complete viral suppression at the first follow-up visit 9 months later, consistent with effective treatment and excellent cART adherence in this sample. This likely reflects the inclusion criteria for the study (stable cART for the previous 6 months at least), and a selection bias for good adherence in these older long-term survivors.

The final model is shown in Figure 1, emphasizing paths related to stigma and its downstream impact on brain health and real-world function. The values for all the direct effects are given in Table S2,http://links.lww.com/QAI/B234 (Supplementary Material). Table 3 shows the direct effects for the stigma and brain health variables that were the conceptual focus of this study. Figure 2 illustrates the relative impact of these variables. The final model fit the data well: $\chi^{2,a}$ = 128.7, df = 70, $p < 0.05^b$; RMSEA[c] = 0.040; SRMR[d] = 0.027; CFI[e] = 0.980; TLI[e] = 0.963.

[a] χ^2 test of exact fit, using the Satorra-Bentler correction for non-normality, and associated degrees of freedom.

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HIV-related stigma had direct effects on cognitive test performance and anxiety. There was also a direct but weaker path from stigma to depression ($p < 0.1$; shown by the dotted line in Fig. 1), retained in the model because the existing literature argues for links between stigma and depression, and between depression and cognition.

Stigma was influenced by HIV-related variables (duration of infection and HIV-specific signs and symptoms). Fig. 1 also shows that duration of HIV and presence of HIV-specific signs (including physical indicators of HIV infection such as changes in body shape) have an impact on other variables in the model such as depression and physical function, separately from their effect on stigma. Poor social support was also a contributor to stigma as well as to depression, anxiety and worse physical function. The influence of stigma on cognitive test performance and mood in turn had widespread downstream effects on real-life function and participation. This included distinct paths from cognitive test performance and anxiety to self-reported cognitive difficulties, and from depression to physical function. Quality of the environment and age affected all ICF model variables, represented in Figure 1 by an arrow to the label "ICF Model". (also see Table S2,http://links.lww.com/QAI/B234)

Figure 2 presents the magnitudes of the effects of the key path parameters relating stigma, brain health and everyday function. These are expressed in standardized units (stdXY) derived from the regression parameters in the path model (see also Table 3 and Table S2,http://links.lww.com/QAI/B234) to allow direct comparison of effects across variables.

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[b] Although the Satorra-Bentler χ^2 was statistically significant, this was offset by the very large sample size and low ratio of the χ^2 to its degrees of freedom (1.8).
[c] A measure of global close fit where values less than 0.05 represent good fit.
[d] A measure of badness of fit based on fitted residuals; values less than 0.05 represent good fit and values to 0.10 represent reasonable fit.
[e] CFI and TLI values greater than 0.95 indicate acceptable fit, 0.97 indicate good fit; both measure fit relative to an independent model, but the TLI includes a correction for model complexity.

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Stigma was most highly associated with anxiety, with cognitive test performance the second strongest association. In turn, cognitive test performance was associated with two variables reflecting everyday cognitive functioning: degree of engagement in meaningful activities and self-reported cognitive difficulties. Of these associations, cognitive test performance had the strongest relationship with self-reported cognitive difficulties. Finally, self-reported cognitive difficulties had effects on social role and, to a somewhat greater extent, life-space mobility. To put the relative magnitude of these stigma and brain health path parameters in context, their strengths ranged from about one-third to one-half of the strongest relationship in the full model (i.e. the path between depression and social role), which had a stdXY of 0.56 (Table S2,http://links.lww.com/QAI/B234).

Discussion

As hypothesized, stigma had a direct effect on cognitive performance, in addition to its effects on mood (anxiety and (more weakly) depression) in this sample of older Caucasian men with well-controlled HIV infection. Through these variables, stigma affected everyday function, including physical function, self-reported cognitive difficulties, and engagement in meaningful activities. Downstream effects were observed for social role and life-space mobility (i.e. the space in which people act, ranging from their own homes outwards to the larger community).

These findings could suggest either that people who report feeling stigmatized due to their HIV status avoid social and community activities or that feelings of stigma arise from being excluded from these activities[36,37]. These cross-sectional data do not allow the direction of the effects to be established. Indeed, the direction may differ across people. For example, in the model here social support (which includes loneliness and social network variables) is shown as

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affecting stigma, but the relationship could be in the opposite direction (stigmatization leading to loneliness). Qualitative studies could clarify these directions and identify variation in experience.

The impact of stigma on mood and other health outcomes replicates the literature in other stigmatized populations (e.g. [38]) as well as in HIV[1,22]. Again, the directionality of these relationships is uncertain, as people with depression may pay more attention to experienced stigma, or ruminate about those events. Recent work has linked poorer cognition with loneliness in people with HIV[39], and stigma could contribute to loneliness.

Our study is novel in that we have shown a direct effect between stigma and cognitive performance in HIV. Multiple mechanisms likely underpin this association, opening avenues for future research on potentially modifiable social-environmental contributors to cognitive difficulties in older people with well-controlled HIV infection. These factors likely have impact beyond the psychosocial realm: Recurrent negative social experience or isolation can have direct effects on brain structure and function, through routes as varied as experience-driven neuroplasticity[17], chronic stress-related inflammation[21], and cerebrovascular injury[40]. These insights suggest points of potential contact between the psychosocial and biological effects of HIV infection, two important but so far largely parallel themes of research in HIV. Stigma can affect cART adherence, in turn leading to greater HIV-related brain injury. However, this is unlikely to be a major factor here, as well over 90% of this sample had consistently undetectable viral load, suggesting excellent adherence.

Strengths of this study include the use of a strong theoretical model and a robust statistical approach ideally suited for high-dimensional, correlated data. Other work using a similar approach to stigma in black Caribbean women living with HIV in Canada reported similar inter-relationships between stigma, social support and depression, as well as with health

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perception, but did not address cognition[25]. We found that quality of the environment, along with age, was important for all variables in the model, including stigma. Interestingly, the oldest men in our cohort expressed less stigma, perhaps reflecting a selection effect into the study, or a survival bias, or both.

This study has limitations. First, inclusion of only Caucasian men limits generalizability. This restriction was planned, to isolate HIV-related stigma from other well-known sources of stigma (gender, race); it seems likely that additional demographic sources of stigma would magnify the effects we observed in this restricted sample, but further work is needed to test this possibility. Guided by our findings, such work could take simpler statistical approaches, requiring smaller samples. Second, stigma was not a primary focus of the main BHN study and was only assessed with a single item. However, the use of an open-ended QOL measure was a planned feature of the main study, and this identified stigma as a uniquely important aspect of QOL in HIV[13], motivating the current analysis of the paths linking stigma and brain health. Future work would benefit from more extensive measurement of stigma; the item we used asked about the person's experience of stigma (i.e. how distressed they are by perceived HIV-related social exclusion) rather than characterizing stigmatizing features of the environment. This item also does not disambiguate constructs such as internalized and anticipated stigma[41]. It would be helpful to assess these facets of stigma in future work, as the literature shows that they may have distinct effects on physical and mental health[1,42], and they may require different stigma reduction strategies. Finally, we assessed cognitive performance with a relatively brief battery of computerized tests. We have shown that these tests can be summarized as a global, continuous measure of cognition reflecting processing speed, attention, memory and aspects of executive

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function relevant to HIV-associated cognitive impairment[3,29]. However, they do not permit classification according to the current HIV-Associated Neurocognitive Disorder nosology.

HIV-related stigma has multiple contributors and widespread repercussions. Here, we show that it has distinct effects on different facets of brain health, notably including cognition. This argues for a broader view of the factors that affect cognition in HIV, pointing to toxic effects of an adverse social environment on the brain. This may not be unique to HIV, with extensive evidence for impact of loneliness and social exclusion on general health and cognitive decline in aging in the general population[40]. This opens promising directions for research and program development aimed at supporting brain health in people living with HIV by intervening on societal factors that contribute to the experience of stigma and personal factors that bolster resilience in the face of such experiences.

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Table and Figure Legends

Table 1: Structure of the measurement model

Table 2: Characteristics of the sample along the ICF model

Table 3: Magnitudes of the effects of path parameters relating stigma, brain health and everyday function for the paths shown in Figure 1. The Table follows the rubrics of the ICF model. Standardized units (stdXY) allow direct comparison of the magnitudes of effects.

Figure 1: Final SEM model (N = 512) for HIV-related stigma based on the ICF model. While the variables within each ICF rubric were allowed to correlate, these correlations are not shown. Paths from stigma are emphasized; all other paths are reported in Table S2. Solid lines indicate significance at $p < 0.05$; the dashed line indicates significance at $p < 0.10$. This weaker relationship was retained as theoretically relevant.

Figure 2: Magnitudes of the effects of the key path parameters relating stigma, brain health and everyday function. These are expressed in standardized units (stdXY), allowing direct comparison.

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Table 1. Structure of the measurement model and overview of the measures. See Table S1 for detailed description of the measures. WHOQOL-HIV BREF (World Health Organization Quality of Life-HIV Bref), HADS (Hospital Anxiety and Depression Scale), RAND-36 MHI (Rand-36 Mental Health Index), B-CAM (Brief Cognitive Ability Measure), PDQ (Perceived Deficits Questionnaire), RAND-36 PFI (Rand-36 Physical Function) CHAMPS (Community Healthy Activities Model Program for Seniors), RAND-36 SF (Rand-36 Social Function).

<table>
<tr><td colspan="5">PERSONAL FACTORS: Age, Education</td></tr>
<tr><td colspan="3">IMPAIRMENTS</td><td rowspan="2">ACTIVITY LIMITATIONS</td><td rowspan="2">PARTICIPATION RESTRICTIONS</td></tr>
<tr><td>HIV-related</td><td>Stigma</td><td>Brain Health</td></tr>
<tr><td>Signs and symptoms</td><td rowspan="3">Beliefs Domain: WHOQOL-HIV BREF</td><td>Depression (HADS, RAND-36 MHI)</td><td>Physical function (RAND-36 PFI)</td><td>Social role (RAND-36 SF)</td></tr>
<tr><td rowspan="2">Duration of HIV infection</td><td>Anxiety (HADS, RAND-36 MHI)</td><td>Cognitive difficulties (PDQ)</td><td rowspan="2">Life-Space Mobility</td></tr>
<tr><td>Cognitive performance (B-CAM)</td><td>Meaningful activities (CHAMPS)</td></tr>
<tr><td colspan="5">ENVIRONMENTAL FACTORS: WHOQOL-HIV Domain V (Environment) and item for social support</td></tr>
</table>

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Table 2 Description of the sample under the ICF rubrics of personal, environmental, and biological factors

	N	Mean	SD or [percent]
Personal factors			

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Age		54.1	8.2
<45	58		[11.4]
45-54	236		[46.4]
55-64	164		[32.2]
≥65	51		[10.0]
Education		-	
Primary school	17		[3.3]
High school	120		[23.5]
College/ Technical	174		[34.1]
University	143		[28.0]
Post-graduate	56		[11.0]
Environmental factors			
Social support (1-5 higher is better)		3.7	1.0
Quality of environment (0-100 higher is better)		72.5	16.7
Impairments			
Duration of HIV infection (y)		17.4	8.0
HIV-specific symptoms (0-30 higher is worse)		6.9	4.8
HIV-related stigma (1-5 higher is worse)		1.7	1.1
RAND-MHI (anxiety questions only, 0-100)		62.0	21.6
HADS (rescaled 0 to 100)		65.9	20.3
Original HADS scoring (0-21 higher is worse)		7.2	
RAND-MHI (depression questions only, 0-100)		70.6	21.6
HADS (rescaled 0 to 100)		78.4	17.8
Original HADS scoring (0-21 higher is worse)		4.5	3.7
B-CAM (0-41 higher is better)		20.3	4.5
Activity Limitations			
RAND-PFI (0-100 higher is better)		82.6	20.3
PDQ (rescaled 0-100 higher is better)		65.6	17.2
Hours of meaningful activity		35.1	32.2
Participation restrictions			
RAND-SF (0-100 higher is better)		82.6	20.3
Life-space mobility (0-8 higher is better)		6.6	1.1

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Personal	Environment	Biology	Stigma	Impairments	Activities	Participation	Direct effect (β)	SE	Standardized (STDXY)
Age			Stigma				-0.014	0.005	-0.104
	Social support		Stigma				-0.151	0.061	-0.133
	Quality of Environment		Stigma				-0.01	0.004	-0.144
		HIV symptoms	Stigma				0.063	0.019	0.14
		Duration of HIV	Stigma				-0.012	0.006	-0.089
			Stigma	Anxiety			-2.821	0.636	-0.176
				Anxiety	Cognitive		0.529	0.045	0.549
				Anxiety	Physical		-0.229[b]	0.139	-0.202
			Stigma	B-CAM			-0.396	0.164	-0.098
				B-CAM	Cognitive		0.987	0.151	0.259
				B-CAM	Meaningful		1.219	0.346	0.17
			Stigma	Depression			-0.992 [a]	0.540	-0.071
				Depression	Physical		0.567	0.183	0.432
				Depression		Social	0.963	0.082	0.563
					Cognitive	Social	0.234	0.061	0.152
					Cognitive	LSM	0.007	0.003	0.109
					Physical	Social	0.175	0.044	0.134
					Physical	LSM	0.005	0.002	0.094

Table 3: Direct effects of model variables, focusing on the paths to and from stigma, organized by the rubrics of the ICF model. The standardized beta (STDXY) allows comparison of the strength of effects across variables. All associations are significant at $p < 0.05$ except the relationship between stigma and depression(a), $p < 0.1$, retained for its theoretical relevance and between anxiety and physical function (b), $p > 0.1$, retained for model fit. Significant direct effects for all variables included in the model are provided in Table S2 (Supplementary Material). SE (standard error).

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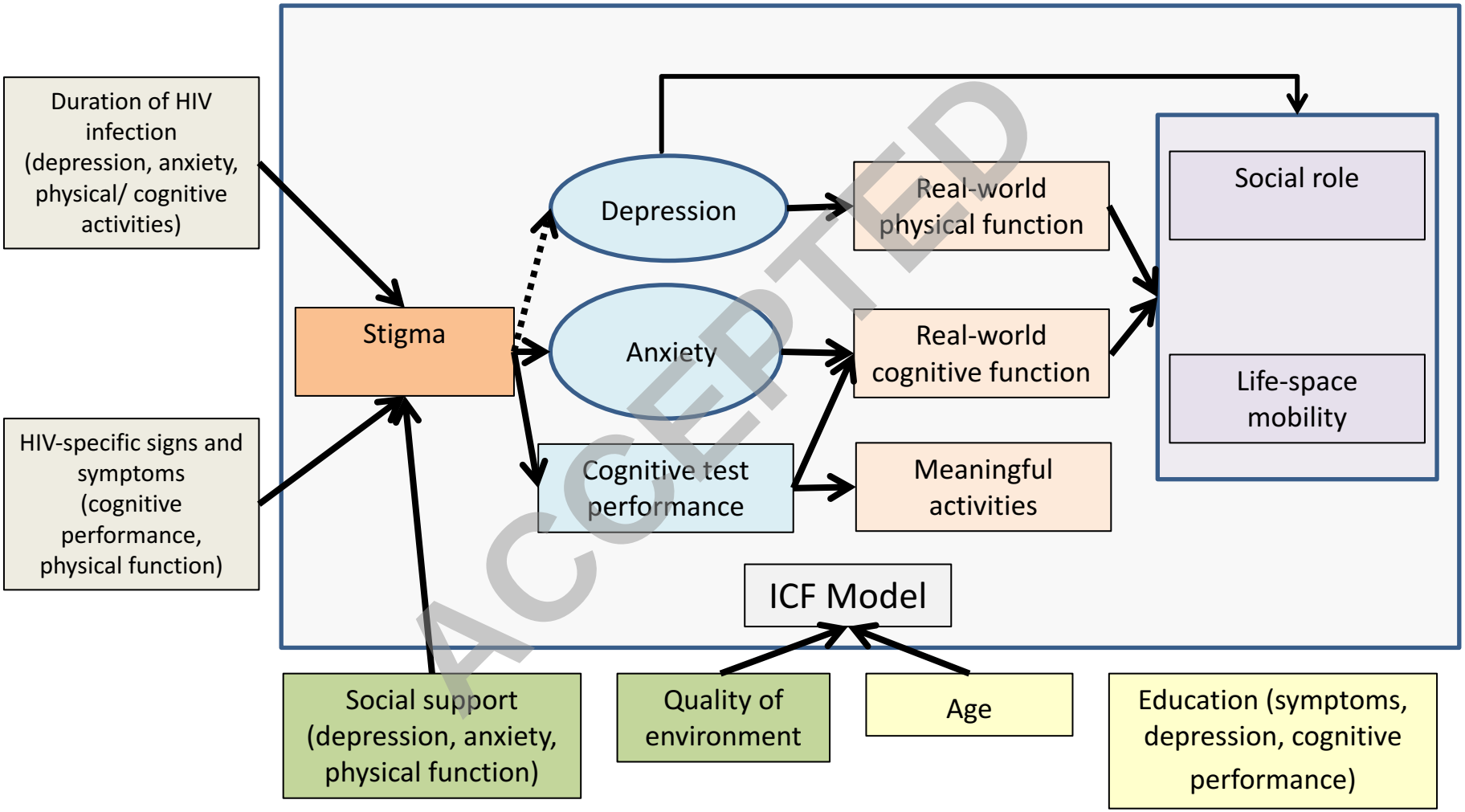

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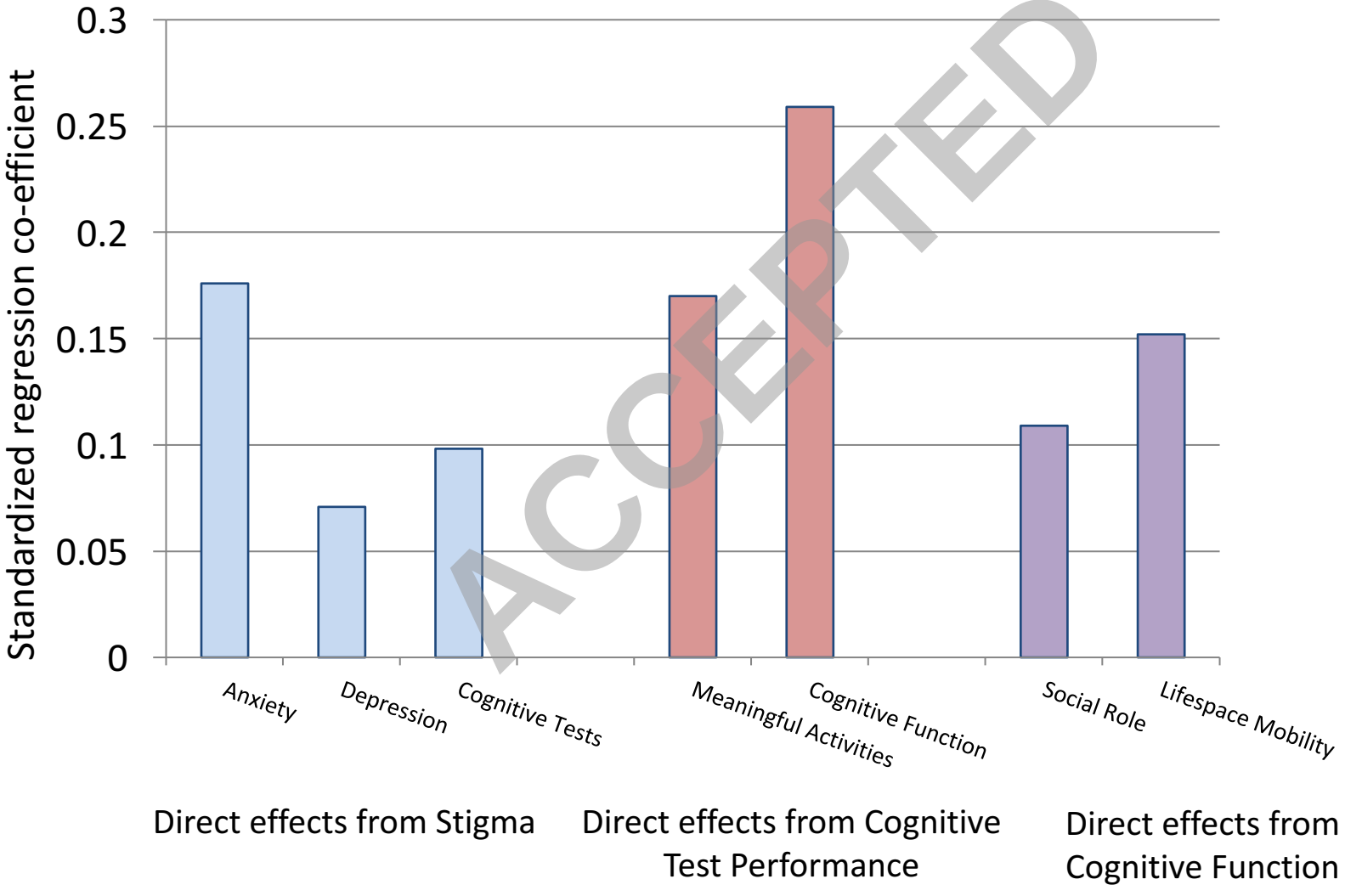
Relative Magnitude of the Effect of Stigma, Cognitive Test Performance, and Real-world Cognitive Function



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