



Amygdalar activity predicts future incident diabetes independently of adiposity

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ABSTRACT

While it is established that psychosocial stress increases the risk of developing diabetes mellitus (DM), two key knowledge gaps remain: 1) the neurobiological mechanisms that are involved in mediating that risk, and 2) the role, if any, that adiposity plays in that mechanism. We tested the hypotheses that: 1) metabolic activity in the amygdala (AmyGA), a key center involved in the neurobiological response to stress, associates with subsequent DM risk, and 2) this association is independent of adiposity. AmyGA and adipose tissue volumes were measured, and serial blood assessments for DM were obtained in 232 subjects who underwent combined ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG-PET/CT) imaging. Higher baseline AmyGA predicted subsequent, new-onset DM, independently of adiposity and other DM risk factors. Furthermore, higher adiposity only increased DM risk in the presence of higher AmyGA. In a separate cross-sectional cohort, higher AmyGA associated with higher insulin resistance. Accordingly, the current study shows, for the first time, that activity in a stress-responsive neural region predicts the onset of DM. Further, we observed that this neurobiological activity acts independently of, but also synergistically with adiposity to increase DM risk. These findings suggest novel therapeutic targets to help manage and possibly prevent DM.

1. Introduction

Diabetes mellitus (DM) represents a rapidly growing threat to global health (Mokdad et al., 2003). The development of DM is closely associated with obesity and, more potently, with excess visceral adipose tissue (VAT) (Neeland et al., 2012). Yet, most obese individuals do not develop DM, underscoring the fact that additional variables contribute

to the development of diabetes (Rosen and Spiegelman, 2006). Psychosocial stress represents such a factor (Pouwer et al., 2010). Epidemiologic evidence suggests that stress adversely impacts glycemic control among individuals with pre-existing DM (Chida and Hamer, 2008) and contributes to the development of DM (Kumari et al., 2004; Mooy et al., 2000). However, the mechanistic pathway that links stress to DM remains incompletely defined.

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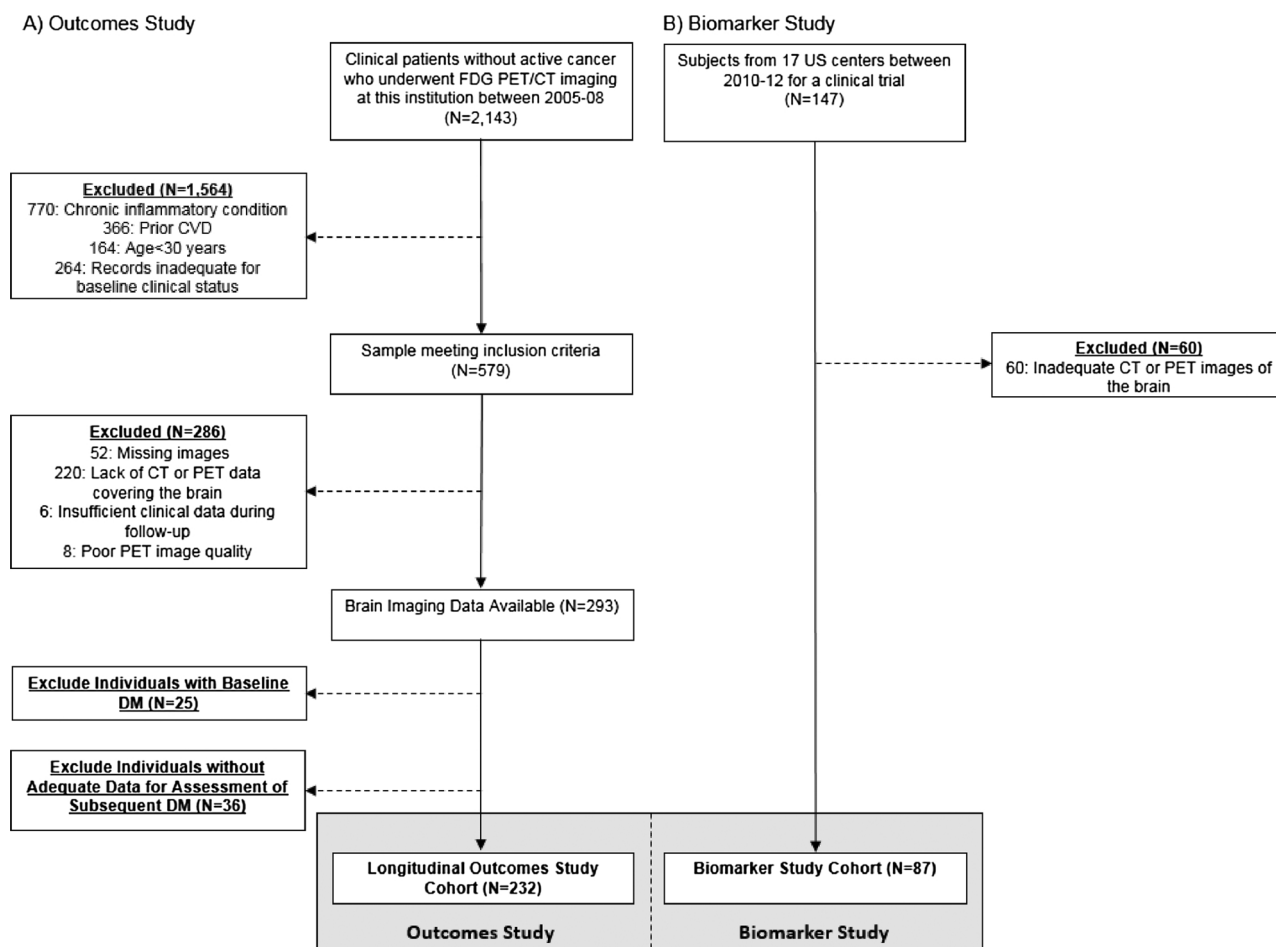


Fig. 1. (A) Outcomes study subject selection. (B) Biomarker study subject selection.

Abbreviations: CVD: cardiovascular disease, CT: computed tomography, DM: diabetes mellitus, FDG: fluorodeoxyglucose, LDL: low density lipoprotein, PET: positron emission tomography.

Stress associates with increased adiposity (notably VAT), in part due to its association with adverse health behaviors, such as excess caloric intake and physical inactivity (Adam and Epel, 2007; Kouvonen et al., 2005). Since increased VAT is a potent risk factor for DM, it would be appealing to simply rely on measurements of VAT to gain insights into the risk of DM in the context of stress. However, prior work raised doubts about the importance of adiposity in mediating the risk of developing DM from stress (Mooy et al., 2000). In that cross-sectional study, although life stressors were associated with DM, adjusting for waist-to-hip ratio only marginally attenuated that association. Moreover, radiographic measures of adiposity (e.g., VAT) were not available. Accordingly, it remains unclear to what degree adiposity mediates the relationship between stress and subsequent DM.

Another key question, regarding the association between stress and DM, is which regional brain areas participate in the pathobiological mechanism. Translation of external stressors to their physiological consequences may involve activation of the brain's salience network, an ensemble of interconnected structures involved in complex functions such as cognition and emotion, among which the amygdala is an important component (Wang et al., 2010). Advanced imaging tools allow objective assessment of signals in brain regions (including the amygdala) that are known to be activated by psychosocial stress and stress conditions. Resting amygdalar metabolic activity (AmygA) can be measured using ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG-PET/CT) (Tawakol et al., 2017). The AmygA signal is reproducible, as indicated by an observed median change of only 2% in a clinically stable population over a three-month

period (Hammad et al., 2017). AmygA associates with anxious temperament in animal models (Oler et al., 2010) and perceived stress in humans (Tawakol et al., 2017), and it is upregulated in chronic stress conditions (e.g., post-traumatic stress disorder, anxiety) (Bremner et al., 2005; Whalen et al., 2002). This signal may also provide important insights into the pathobiological consequences of stress, in that increased AmygA has previously been shown to robustly predict incident cardiovascular disease events in humans (Tawakol et al., 2017). Therefore, of the several brain regions potentially involved in the neurobiological response to stress, we prospectively hypothesized that the amygdala plays an important role in the mechanism linking chronic stress to DM.

^{18}F -FDG-PET/CT imaging is uniquely suited for investigating the relationship between the neurobiological response to stress and metabolic disease, since it enables simultaneous measurement of regional brain metabolic activity, using ^{18}F -FDG-PET, and volumetric measures of adipose tissues (e.g., VAT), using CT (Figuerola et al., 2016). Accordingly, we employed these imaging techniques and assessed for the development of new-onset type 2 DM to determine whether: 1) increased AmygA associates with subsequent new-onset DM and 2) this association is independent of adiposity.

2. Materials and methods

2.1. Overview

The study findings derive from two separate cohorts: 1) a

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