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First biological marker for major depression could enable better diagnosis and treatment

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Teenage boys who show a combination of depressive symptoms and elevated levels of the 'stress hormone' cortisol are up to fourteen times more likely to develop major depression than those who show neither trait, according to research funded by the Wellcome Trust.

In a study published today in the *Proceedings of the National Academy of Sciences*, researchers from the University of Cambridge have identified the first biomarker – a biological signpost – for major, or clinical, depression. They argue that this could help identify those boys in particular at greatest risk of developing the illness and provide treatment at an earlier stage.

Major, or clinical, depression is a debilitating mental health problem that will affect one in six people at some point in their lives. However, until now there have been no biomarkers for major depression; this is believed to be, in part, because both the causes and the symptoms can be so varied.

"Depression is a terrible illness that will affect as many as ten million people in the UK at some point in their lives," says Professor Ian Goodyer from the University of Cambridge, who led the study. "Through our research, we now have a very real way of identifying those teenage boys most likely to develop clinical depression. This will help us strategically target preventions and interventions at these individuals and hopefully help reduce their risk of serious episodes of depression and their consequences in adult life."

Dr Matthew Owens from the University of Cambridge, first author on the study, adds: "This new biomarker suggests that we may be able to offer a more personalised approach to tackling boys at risk for depression. This could be a much needed way of reducing the number of people suffering from depression, and in particular stemming a risk at a time when there has been an increasing rate of suicide amongst teenage boys and young men."

The researchers measured levels of cortisol in saliva from two separate large cohorts of teenagers. The first cohort consisted of 660 teenagers, who provided four early morning samples on schooldays within a week and then again twelve months later. The researchers were able to show within this cohort that cortisol levels were stable over one year in the population at large in both boys and girls.

A second cohort, consisting of 1,198 teenagers, provided early morning samples over three school days.

Using self-reports about current symptoms of depression collected longitudinally over the twelve months and combining these with the cortisol findings, Professor Goodyer and colleagues were able to divide the teenagers in the first cohort into four distinct sub-groups, ranging from those with normal levels of morning cortisol and low symptoms of depression over time (Group 1) through to those teenagers with elevated levels of morning cortisol and high symptoms of depression over time (Group 4) – this latter group made up one in six (17%) of all subjects. Importantly, the research group replicated exactly these sub groups using the second cohort.

Because the two cohorts gave identical results, Professor Goodyer and colleagues were able to combine them and study the whole sample of 1,858 teenagers for the probability of developing clinical major depression and other psychiatric disorders when followed up 12 to 36

months later.

The subjects in Group 4 were on average seven times more likely than those in Group 1, and two to three times more likely than in the other two groups, to develop clinical depression. Further analysis revealed that boys in Group 4 were fourteen times more likely to suffer from major depression than those in Group 1 and two to four times more likely to develop the condition than either of the other two groups. Girls in Group 4, on the other the other hand, were only four times more likely than those in Group 1 to develop major depression, but were no more likely to develop the condition than those with either elevated morning cortisol or symptoms of depression alone. The findings suggest gender differences in how depression develops.

In order to demonstrate that the combination of high levels of cortisol and depressive symptoms was indeed a biomarker for a particular type of depression, the researchers needed to show that the teenagers in Group 4 were different from those in the other groups. They demonstrated this using a memory test completed on the first cohort consisting of systematically recording episodes recollected from an individual's life (known as 'autobiographical memory') under standardized test conditions.

Both boys and girls in Group 4 were particularly poor at systematically recollecting specific autobiographical memories from over thirty example situations across different social and personal domains. For example, when given the word 'picnic', most teenagers give a fairly detailed account of a time when they went on a picnic and who they were with; in Group 4, individuals tended to give very little, and more general non specific, information. This supports evidence from the scientific literature that suggests that high cortisol acts to suppress autobiographical memory recall.

The researchers hope that having an easily measurable biomarker – in this case, elevated cortisol plus depressive symptoms – will enable primary care services to identify boys at high risk and consider new public mental health strategies for this subgroup in the community.

The research has been welcomed by the Wellcome Trust, which funded the study. Dr John Williams, Head of Neuroscience and Mental Health, says: "Progress in identifying biological markers for depression has been frustratingly slow, but now we finally have a biomarker for clinical depression. The approach taken by Professor Goodyer's team may yet yield further biomarkers. It also gives tantalising clues about the gender differences in the causes and onset of depression."

More information: Owens, M et al. Elevated morning cortisol is a stratified population level biomarker for major depression in boys only with high depressive symptoms. *PNAS*; e-pub 17 Feb 2014. www.pnas.org/cgi/doi/10.1073/pnas.1318786111

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