Stroke Center West:
Translational stroke research - networking workshop

Physical exercise and antidepressants in common mental disorders in relation to stroke

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Outline

- ## Background
  - Personal background
  - Physical activity and antidepressants – synergies?
  - Physical activity and common mental disorder (anxiety / depression / other)
    - Prestroke
    - Poststroke

- ## Research questions
- ## Methods
- ## Results
- ## Discussion

Personal background

- Preclinical dissertation on astrocyte communication

- Preclinical studies on IGF-I, GH effects on brain

- IGF-I, insulin resistance, cytokines after clinical stroke.

- IGF-I and physical exercise

- Physical exercise and life-style factors
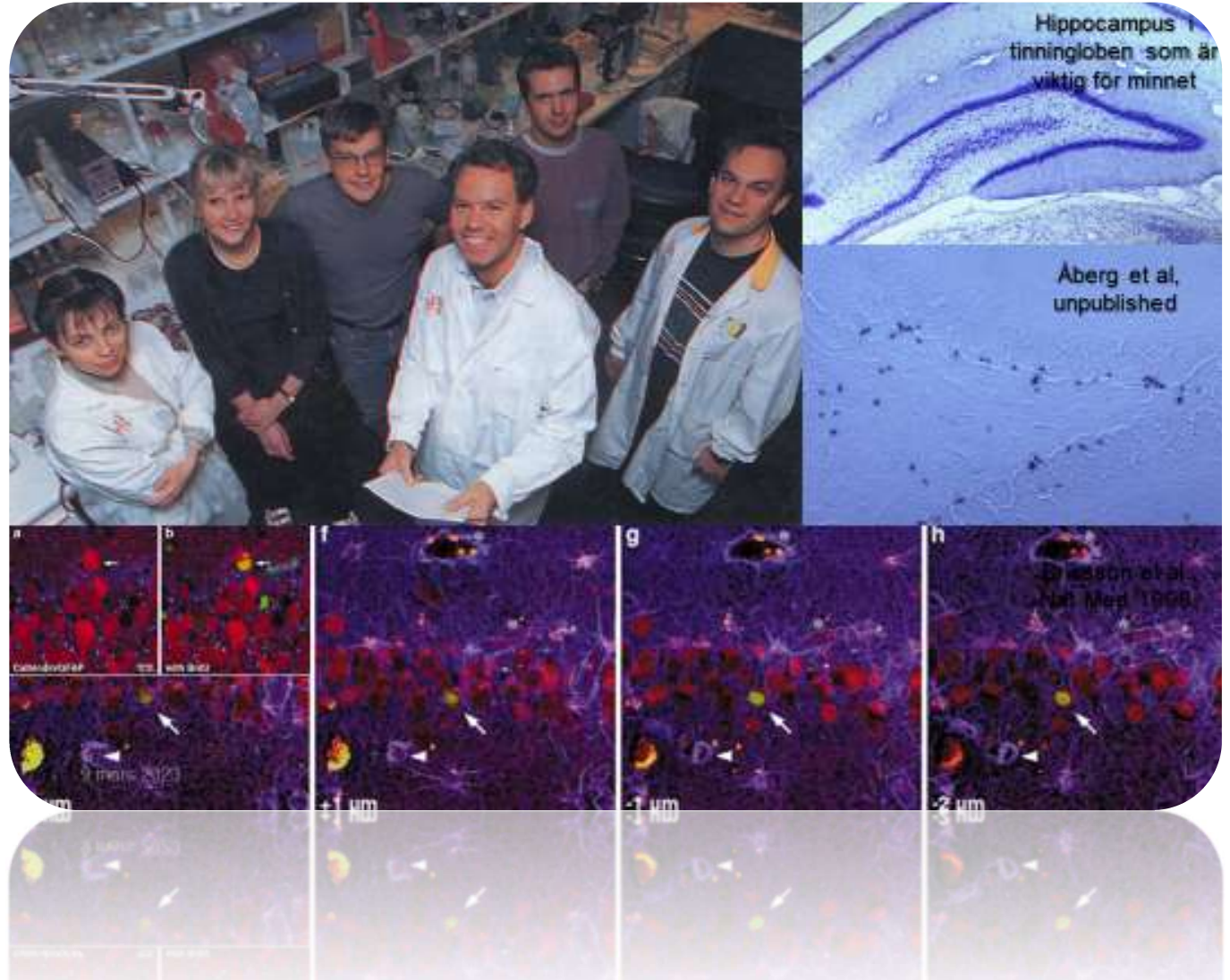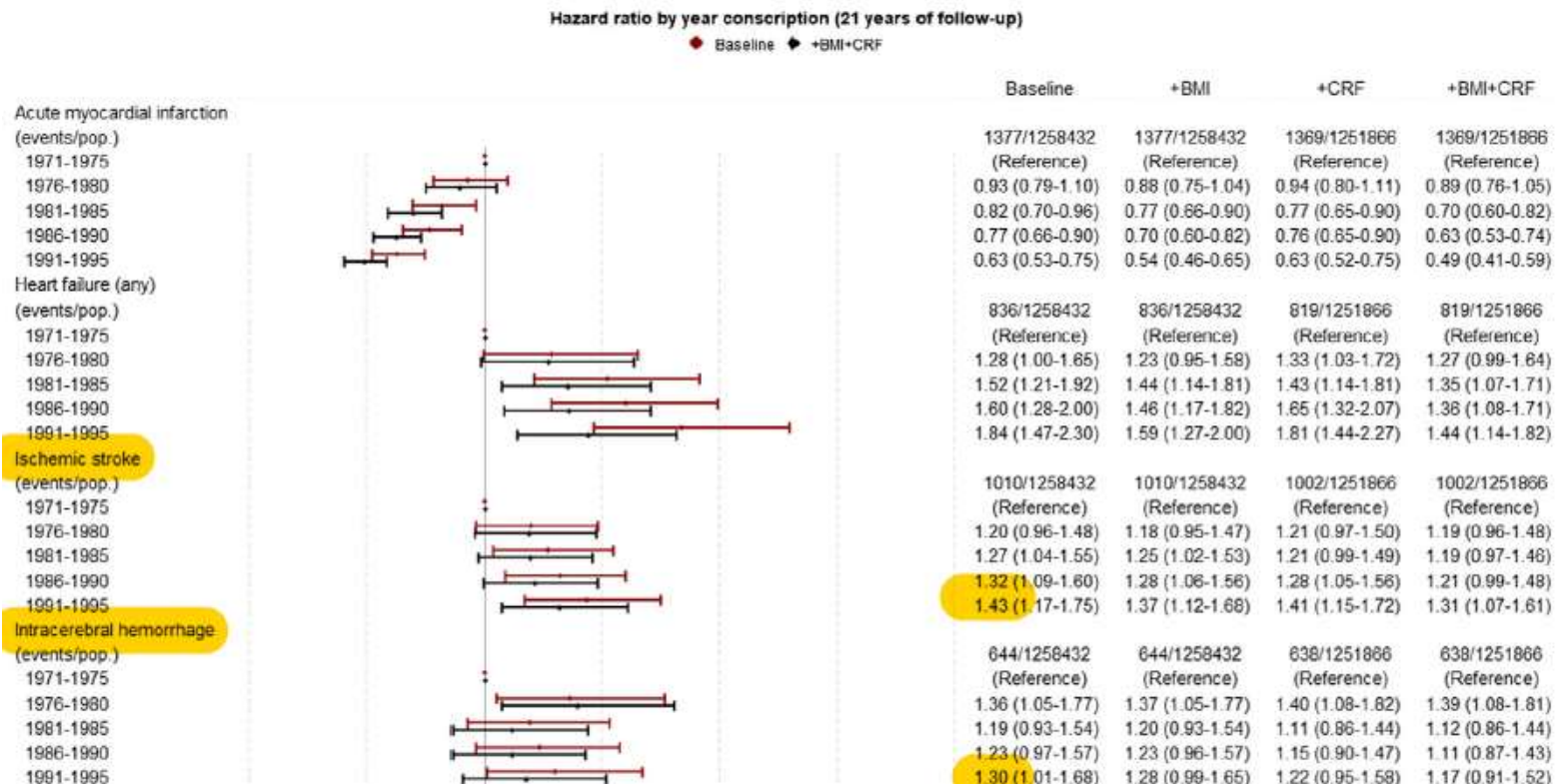
Young stroke increases…

- Adjusted incidence increases for young women (50-90%), and young men (20-40%) until 2010.

- This increase continues from 1995 to 2016 in young males (born in 1971 to 1995).

1. Rosengren A, Stroke. 2013. PMID: 23839506.
2. Åberg-ND. 2021. J Internal Med. PMID 33826195

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Physical activity and antidepressants – synergies?

Physical activity and antidepressants – synergies?

A meta-analysis with 10 publications

- On top of standard treatment,

- Aerobic exercise and even more so,

- Strength exercise reduce depressive symptoms

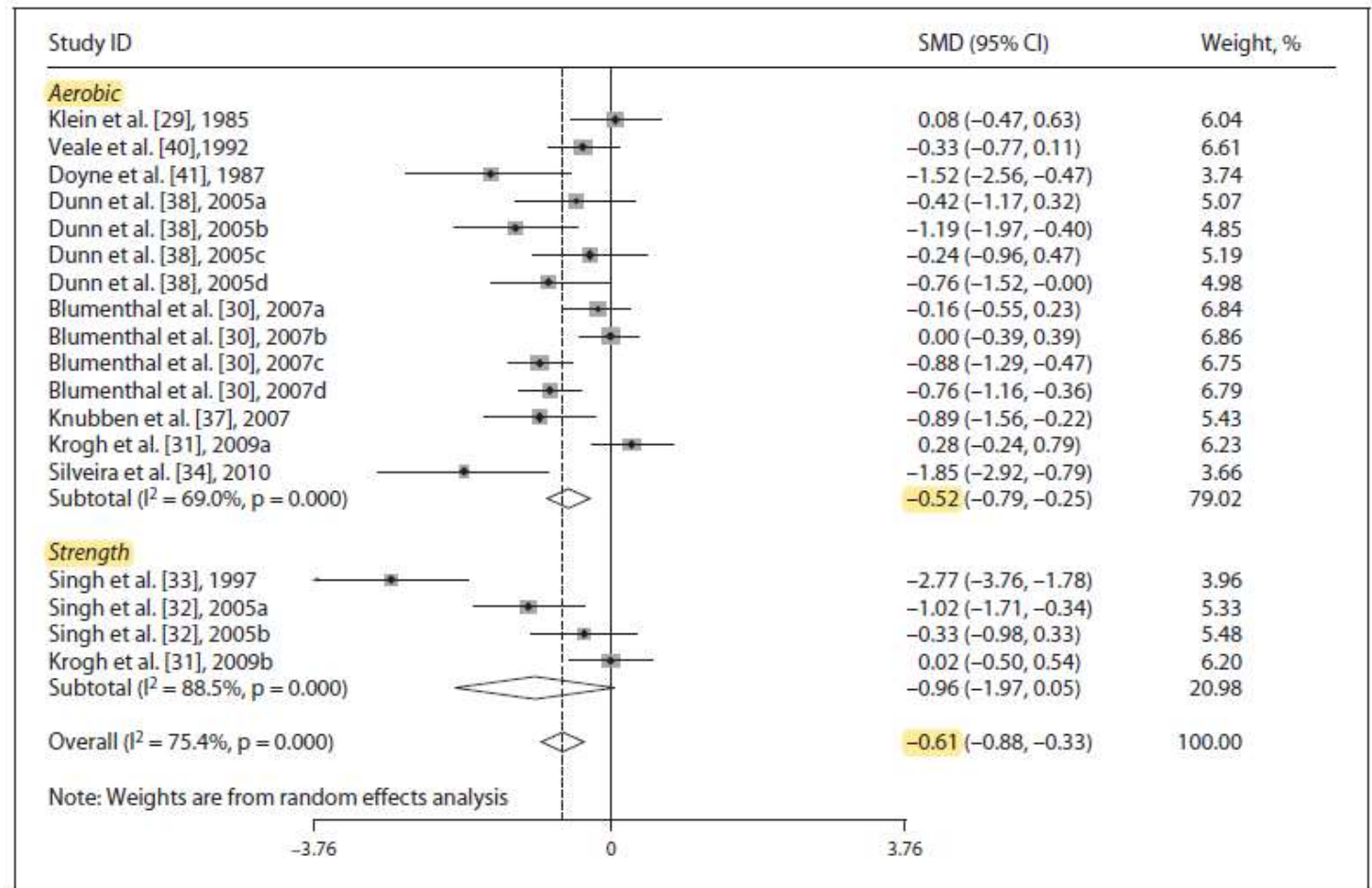
Fig. 2. Meta-analysis of studies assessing the effect of exercise in patients with clinically diagnosed depression by intervention.
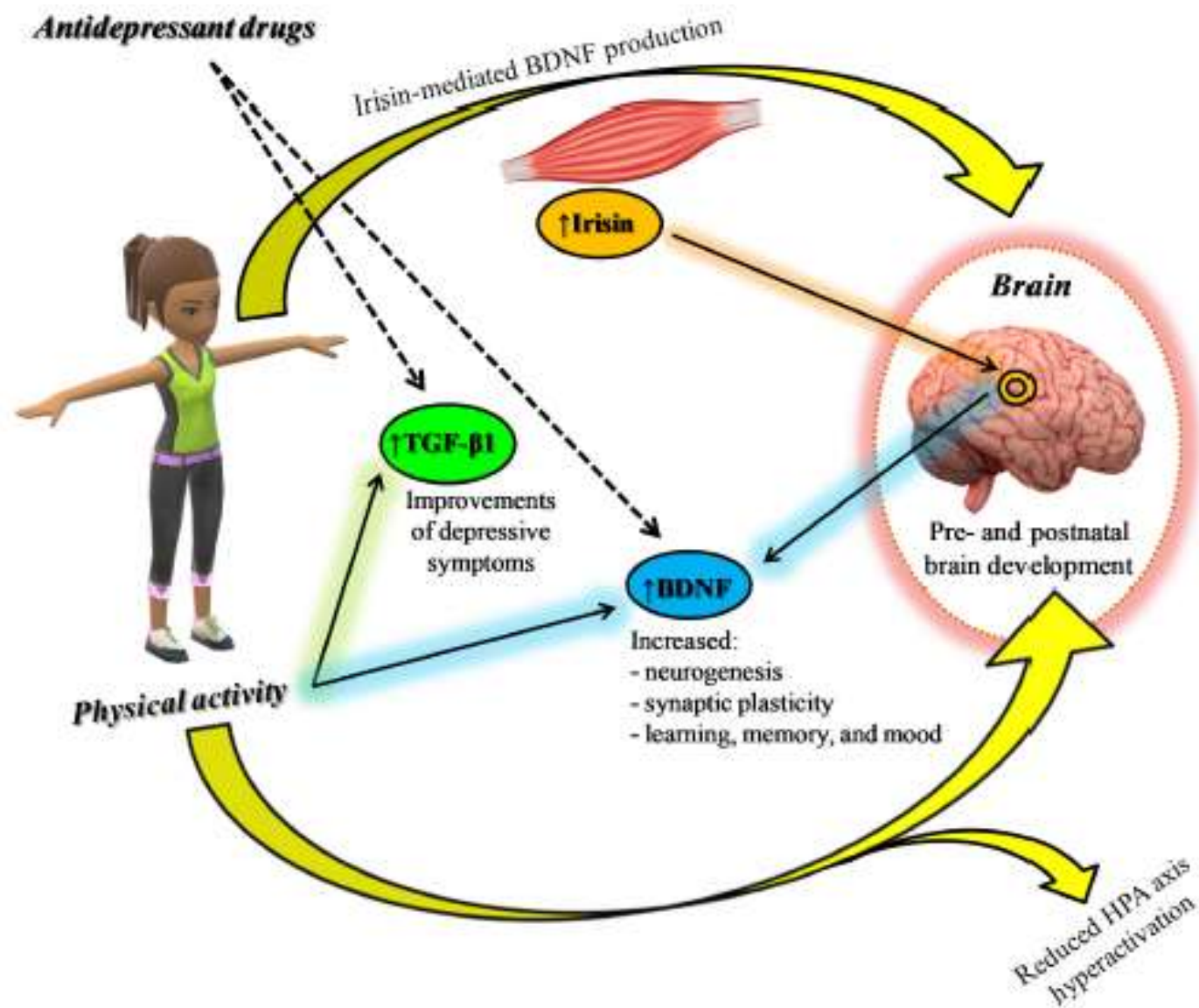
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FIGURE 2 | Synergic effect between physical activity and antidepressants: positive modulation of neurotrophic factors.

# Prestroke physical activity and subsequent stroke risk

Aerobic fitness at age 18 and future stroke

Low aerobic fitness

- Increases risk of any stroke 1.7 times
- Increases risk of fatal stroke 2.5 times

Low muscle strength

- Increased risk of any stroke is about 50% of that of low aerobic fitness
- The effect of low muscle strength is robustly attenuated by low aerobic fitness
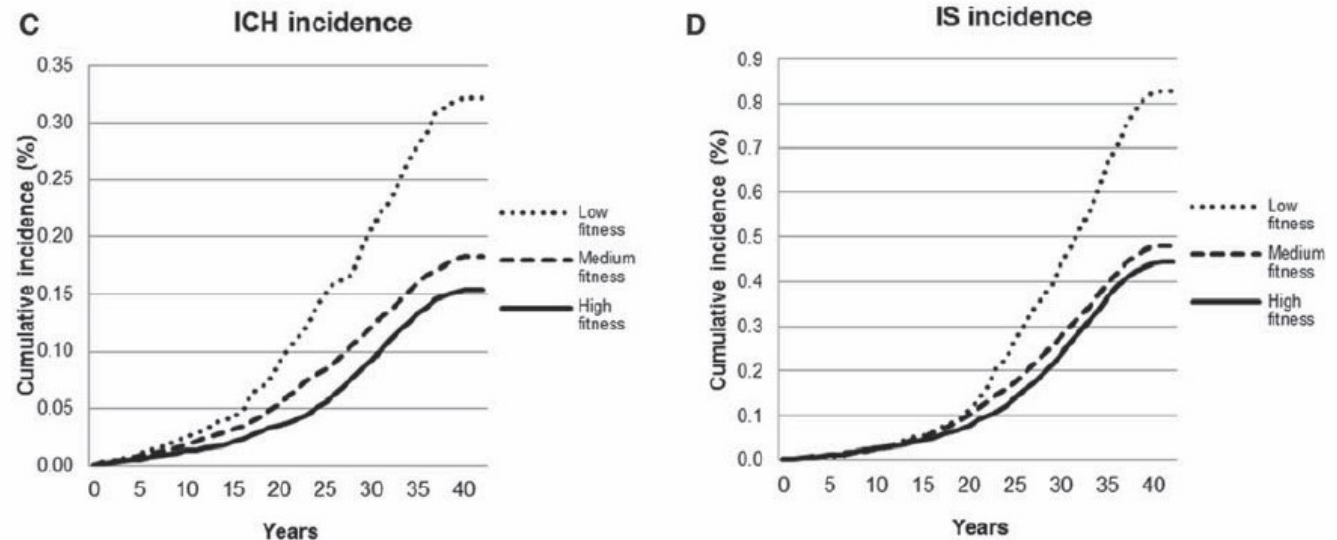
Numbers of stroke (5-year intervals) and numbers exposed (beginning of each 5-year interval)

Years	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-42
Exposed (n)	1165358	1128533	1068633	979017	856538	686745	474068	215591	20161
All stroke (n)	345	561	840	1147	1591	1993	2422	1829	189
SAH (n)	16	44	41	67	124	125	142	80	9
ICH (n)	63	96	124	213	314	409	486	321	30
IS (n)	79	154	251	451	767	1133	1434	1188	121

Abbreviations: Subarachnoid hemorrhage (SAH), Intracerebral hemorrhage (ICH), Ischemic stroke (IS)

Åberg, 2015, Stroke . PMID: 26060247

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Depression is a risk factor for stroke

- **Meta-analysis:**
  - Pan A et al. JAMA. 2011 PMID: 21934057
  - 28 prospective cohort studies
  - 317 540 participants
  - 8478 stroke cases
  - Follow-up: 2-29 years

- **Depression**
  - has an overall OR 1.45 for "any stroke"

Figure 2. Adjusted Hazard Ratios of Total Stroke for Depressed Participants Compared with Nondepressed Participants

Study	HR (95% CI)	Weight, %
Vogt et al,[19] 1994	1.19 (0.82-1.75)	3.76
Wassertheil-Smoller et al,[20] 1996	0.86 (0.45-1.65)	2.12
Everson et al,[21] 1998	1.55 (0.97-2.47)	3.11
Simons et al,[16] 1998	1.41 (1.01-1.96)	4.15
Whooley and Browner,[17] 1998	1.70 (0.80-3.50)	1.77
Jonas and Mussolino,[22] 2000	1.73 (1.30-2.31)	4.53
Larson et al,[23] 2001	2.67 (1.08-6.63)	1.30
Ohira et al,[24] 2001	1.90 (1.10-3.50)	2.45
Ostir et al,[25] 2001	1.30 (0.85-1.99)	3.41
May et al,[26] 2002	1.26 (0.85-1.85)	3.68
Yasuda et al,[27] 2002	3.62 (1.12-11.70)	0.85
Wassertheil-Smoller et al,[28] 2004 (no CVD)	1.01 (0.78-1.30)	4.81
Wassertheil-Smoller et al,[28] 2004 (in CVD)	1.45 (1.11-1.90)	4.70
Gump et al,[29] 2005	1.48 (0.93-2.36)	3.12
Avendano et al,[30] 2006 (65-74 y)	3.05 (1.63-5.70)	2.22
Avendano et al,[30] 2006 (>74 y)	0.95 (0.46-1.98)	1.80
Stürmer et al,[31] 2006	1.53 (0.83-2.80)	2.31
Arbelaez et al,[32] 2007	1.25 (1.02-1.53)	5.27
Kawamura et al,[33] 2007	1.25 (0.82-1.90)	3.44
Salaycik et al,[34] 2007 (<65 y)	3.59 (1.76-7.33)	1.86
Salaycik et al,[34] 2007 (>65 y)	0.93 (0.59-1.47)	3.18
Bos et al,[35] 2008	1.21 (0.80-1.83)	3.49
Lee et al,[36] 2008	5.43 (3.47-8.51)	3.24
Liebetrau et al,[37] 2008	2.60 (1.50-4.60)	2.55
Surtees et al,[38] 2008	1.08 (0.67-1.75)	3.03
Whooley et al,[39] 2008	1.47 (0.70-3.11)	1.75
Wouts et al,[40] 2008	1.15 (0.76-1.73)	3.51
Glymour et al,[41] 2010	1.25 (1.12-1.39)	5.95
Nabi et al,[42] 2010	0.87 (0.57-1.32)	3.45
Peters et al,[43] 2010	1.82 (1.19-2.78)	3.41
Pan et al,[18] 2011	1.29 (1.13-1.48)	5.78
Overall ($I^2 = 66.0\%$, $P < .001$)	1.45 (1.29-1.63)	100.00

Hazard Ratio (95% CI) 0.5 1.0 8

Pan A et al. JAMA. 2011 PMID: 21934057

Aerobic fitness, depression and future stroke

- 18-year-old conscripting Swedish men with 5-42-year follow-up (1.2 million).

- Non-psychotic disorders (NPD)
  - Depressive disorders, n=1599.
  - Neurotic / adjustment disorders, n=33 542.
  - Personality disorders, n=6976:
  - Alcohol-related disorders, n=2200.
  - Other substance use disorders, n=11 150.
  - There were some overlap in ICD codes.

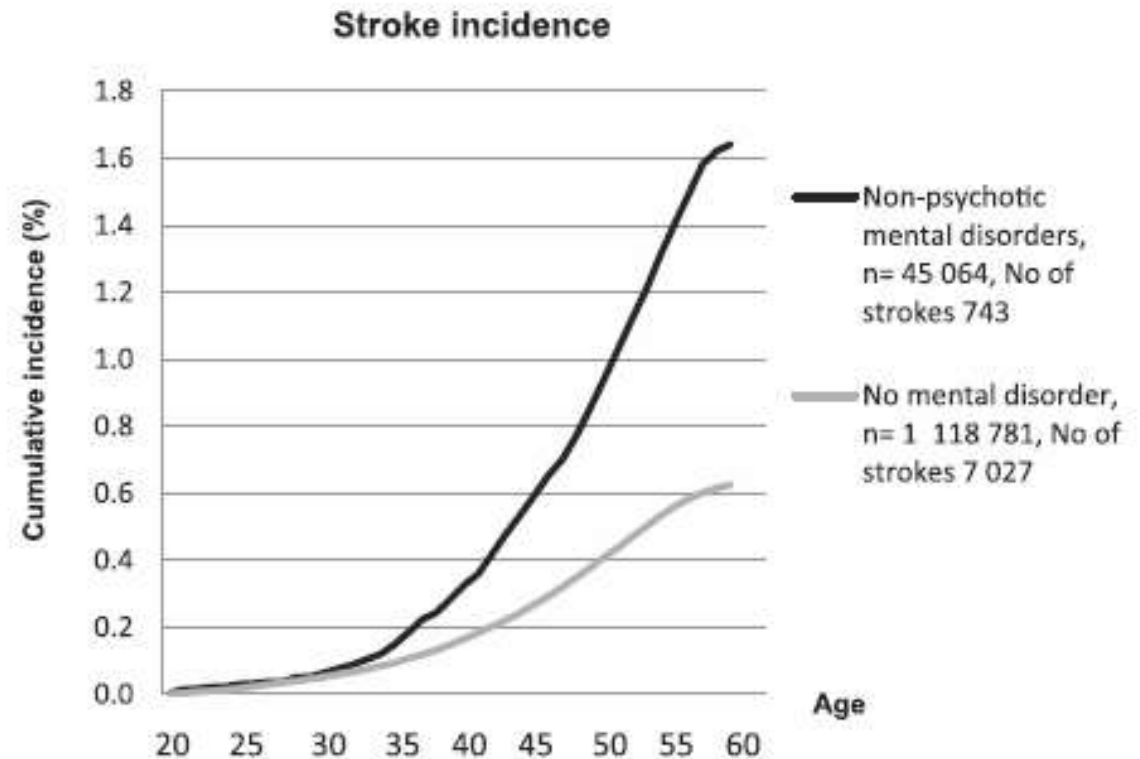- All ischemic and hemorrhagic stroke during follow-up
  - N=743 in NPD
  - N=7042 in healthy 18-year-olds

Stroke incidence

Non-psychotic mental disorders, n= 45 064, No of strokes 743

No mental disorder, n= 1 118 781, No of strokes 7 027

Figure. Cumulative incidence (%) of early stroke of any type in men with and without nonpsychotic mental disorder at the age of 18 years.

Åberg et al., Stroke 2016. PMID: 26846861

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High aerobic fitness attenuates risk for any stroke by non-psychotic or depressive symptoms

Table 5. Importance of IQ and Fitness for Future Stroke Risk Among Young Men Diagnosed With Nonpsychotic Mental Disorder at the Age of 18 Years

	HR (95% CI)				PAR Estimate
	Adjusted,* n=7741	Adjusted,† n=7737	Adjusted,‡ n=7741	Adjusted,§ n=7732	Adjusted,§ n=7732
HRs for all stroke, n=7770					
No mental disorder (n=1 118 781)	1.00	1.00	1.00	1.00	
Nonpsychotic disorders (n=45 064)	1.54 (1.43–1.66)	1.42 (1.32–1.54)	1.39 (1.29–1.50)	1.26 (1.15–1.38)	0.02 (0.01–0.03)
No depressive/neurotic disorders (n=1 128 704)	1.00	1.00	1.00	1.00	
Depressive/neurotic disorders (n=35 141)	1.38 (1.26–1.51)	1.30 (1.17–1.40)	1.24 (1.13–1.36)	1.08 (0.97–1.20)	NA
No personality disorders (n=1 156 869)	1.00	1.00	1.00	1.00	
Personality disorders (n=6976)	1.59 (1.36–1.87)	1.44 (1.23–1.69)	1.44 (1.23–1.69)	1.30 (1.11–1.52)	0.005 (0.001–0.01)
No alcohol/substance use (n=1 150 495)	1.00	1.00	1.00	1.00	
Alcohol/substance use (n=13 350)	1.61 (1.42–1.83)	1.50 (1.31–1.70)	1.46 (1.28–1.66)	1.40 (1.23–1.59)#	0.01 (0.005–0.01)
Stratifications for all stroke, n=7770	Adjusted,* n=7741	Adjusted,† n=7737	Adjusted,‡ n=7741	Adjusted,¶ n=7732	Adjusted,¶ n=7732
No mental disorder (n=1 118 781)	1.00	1.00	1.00	1.00	
High fitness/Nonpsychotic disorders (n=5436)	1.14 (0.90–1.46)	1.08 (0.84–1.38)	NA	1.02 (0.75–1.37)	NA
Medium fitness/Nonpsychotic disorders (n=25 547)	1.42 (1.28–1.58)	1.35 (1.21–1.49)	NA	1.29 (1.14–1.46)	0.02 (0.01–0.03)
Low fitness/Nonpsychotic disorders (n=14 081)	1.50 (1.31–1.72)	1.42 (1.24–1.62)	NA	1.35 (1.15–1.59)	0.05 (0.02–0.08)
Depressive/neurotic disorders					
High fitness/depressive neurotic (n=4264)	1.04 (0.77–1.39)	0.98 (0.73–1.32)	NA	0.90 (0.64–1.26)	NA
Medium fitness/depressive neurotic (n=19 829)	1.22 (1.07–1.38)	1.16 (1.02–1.32)	NA	1.04 (0.90–1.20)	NA
Low fitness/depressive neurotic (n=10 880)	1.43 (1.23–1.67)	1.36 (1.16–1.58)	NA	1.26 (1.06–1.49)	0.03 (0.003–0.05)

*Model A: adjusted for age, decade, conscription test center, BMI.

†Model B: adjusted for age, decade, conscription test center, BMI, IQ.

‡Model C: adjusted for age, decade, conscription test center, BMI, fitness.

§Model D: adjusted for age, decade, conscription test center, BMI, alcohol/substance use, systolic and diastolic blood pressures, IQ, fitness.

¶Model E: adjusted for age, decade, conscription test center, BMI, alcohol/substance use, systolic and diastolic blood pressures, IQ.

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Poststroke physical activity and subsequent depression

Poststroke depression (PSD) is common – a meta-analysis

- 43 studies with 20 293 patients
- Overall prevalence of depression is about 29% (95% CI 25-32), remaining stable up to 10 years after stroke.
- Cumulative incidence of 39-52% within 5 years of stroke.
- 28% (95% CI 23–34), <1 month
  31% (95% CI 24–39), 1–6 months
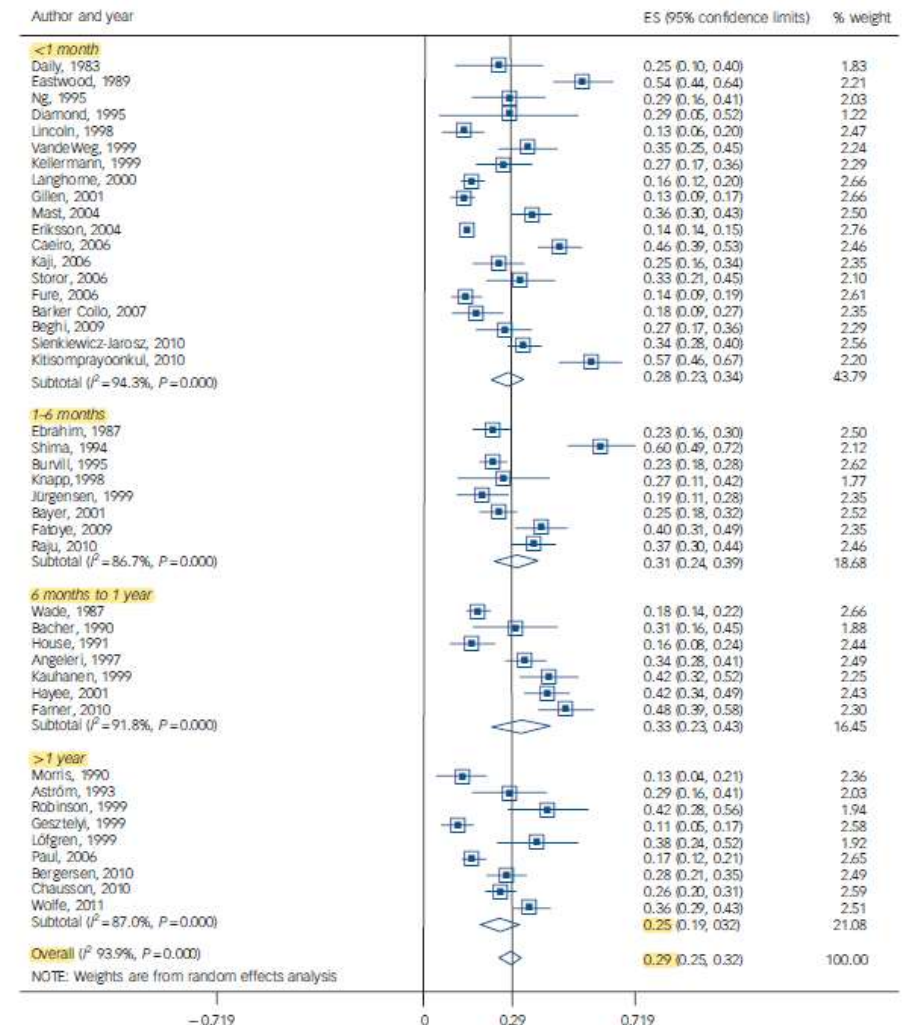- 33% (95% CI 23–43), 6 months to 1 year
- 25% (95% CI 19–32), >1 year

Fig. 2 Pooled prevalence of depression stratified by length of follow-up.

AyerbeL. Br J Psychiatry. 2013. PMID: 23284148.

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Research questions

Research questions

- How does a 12-week physical activity intervention affect anxiety patients functionally, with or without antidepressant treatment?

- How does prestroke lifestyle factors (aerobic fitness, muscle strength, BMI) at age 18 prime or affect later-life poststroke depressive symptoms?

Methods

Methods

- Randomized clinical trial (RCT) "Physical Fitness and Brain - an Interventional study" (PHYSBI, N=286, 2017-2022).
    - A 3-month PE intervention guided by physiotherapists in anxiety patients.
    - Baseline parameters: anthropometry, medications, including antidepressants.
    - Outcomes: Anxiety and depressive scores. EQ-5D quality of life score. Cognitive scores. Sick leave. Work ability.
- Physical Fitness and Brain- Epidemiological studies (PHYSBE)
    - Includes young men from the Swedish Conscription Register
    - Born 1950-87 who enlisted in 1968–2005, N=1958445. Index age 18.3 years
    - Index BMI, blood pressure, aerobic and muscle fitness, and cognition.
    - Education, occupation, and income were obtained from the Longitudinal Integrated Database for Health Insurance and Labor Market Studies (LISA).
    - The follow-up time is up to 51 years until 2019-12-31

Results

Antidepressants interacts with exercise

Figure 1
EQ5D-VAS scores in PHYSBI participants with no antidepressants

Controls vs exercise intervention 12 weeks.
Removed, unpublished data

Figure 2
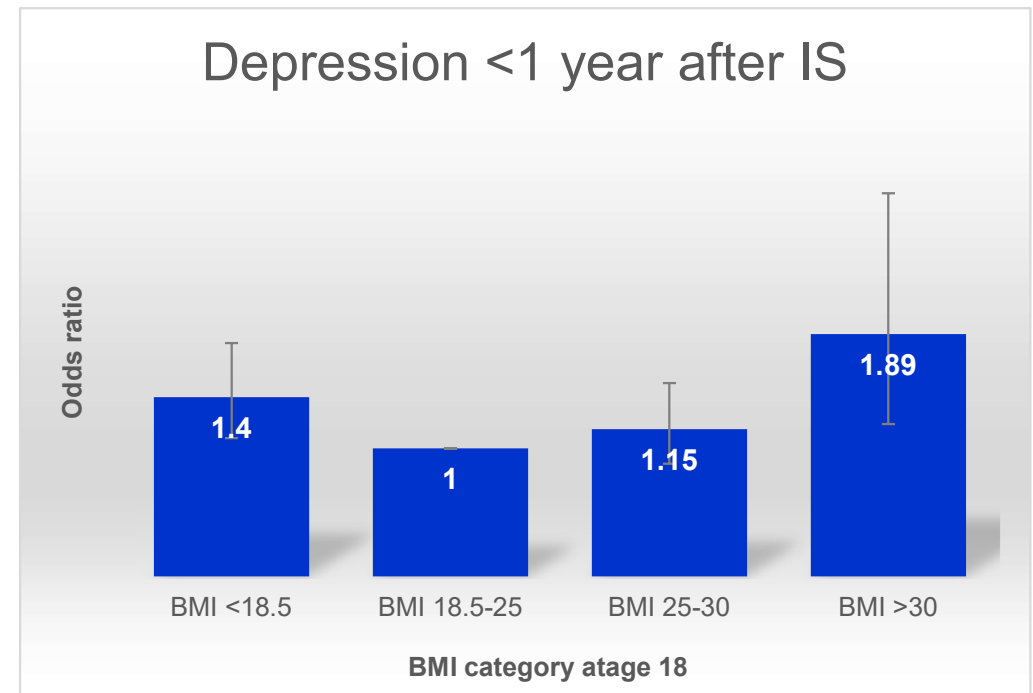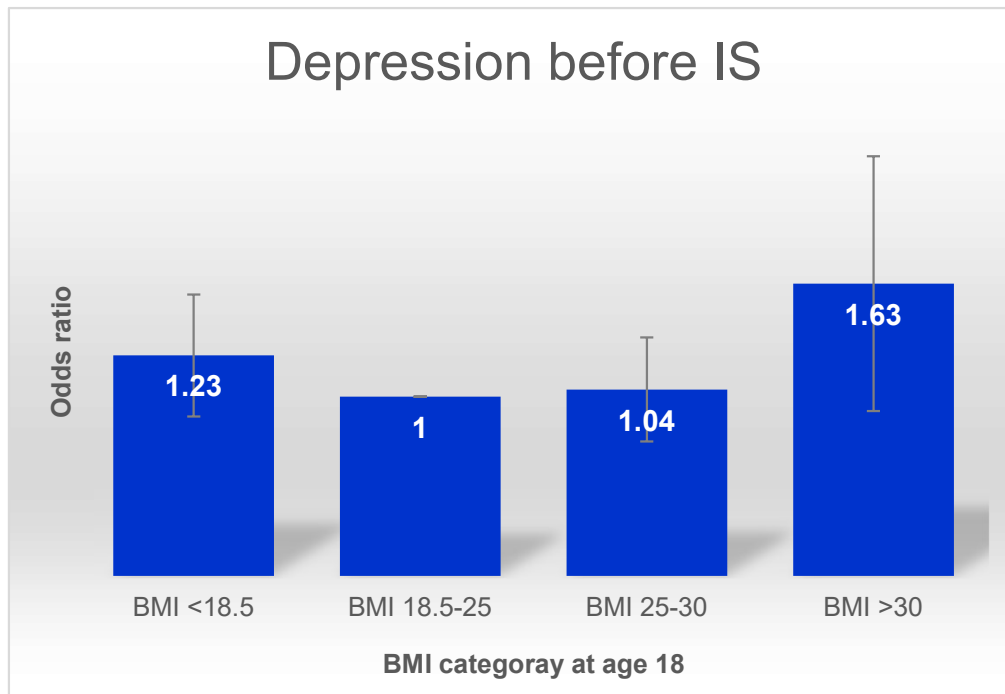EQ5D-VAS scores in PHYSBI participants with antidepressants

Controls vs exercise intervention 12 weeks.
Removed, unpublished data

Outcomes:

- Self-rated quality of life (EuroQol 5 dimensions [EQ-5D] visual analog scale [VAS], score 0-100).
- Significant interaction between exercise and antidepressant medication (p=0.037)
- The difference withstood adjustments for different baseline scores.
- Work ability similar appearance.
- Sick leave similar appearance but not significant

Ischemic strokes associate with prestroke BMI, but even more so with poststroke depression

Depression before IS

Odds ratio

1.23 (BMI <18.5)
1 (BMI 18.5-25)
1.04 (BMI 25-30)
1.63 (BMI >30)

BMI categoray at age 18

Depression <1 year after IS

Odds ratio

1.4 (BMI <18.5)
1 (BMI 18.5-25)
1.15 (BMI 25-30)
1.89 (BMI >30)

BMI category atage 18

- Preliminary data, unadjusted
- N=1401462 with complete data
- N=2402 depression, N=21442 ischemic stroke

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Discussion - summary

- Exercise intervention improves self-rated quality of life in anxiety patients, almost exclusively in those with antidepressant treatment

    - Social factors?
    - No mediation by changes in aerobic fitness, and only minor mediation by change in muscle strength.

- May there be a similar mechanism in stroke patients, either by prestroke priming or concomitant poststroke medications?

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Tack för uppmärksamheten!