

The burden of Group B *Streptococcus* worldwide for pregnant women, stillbirths and children

Paper 10: Neurodevelopmental impairment in children after Group B *Streptococcus* disease worldwide: systematic review and meta-analyses

Supplementary information

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Table S1a: Group B *Streptococcus* syndrome definitions

GBS Syndrome	Definition	ICD-10 code
Possible serious bacterial infection (pSBI)	Any one of the following: a history of difficulty feeding, history of convulsions, movement only when stimulated, respiratory rate of 60 breaths per min or more, severe chest indrawing, temperature $\geq 37.5^{\circ}\text{C}$ or $\leq 35.5^{\circ}\text{C}$ [1]	P35-P39
Sepsis	Clinical signs of pSBI <i>and</i> GBS-positive blood culture or PCR or latex agglutination	P36.0
Meningitis	Clinical signs of pSBI <i>and</i> [GBS-positive CSF culture or PCR or latex agglutination <i>or</i> (GBS-positive blood culture or PCR or latex agglutination <i>and</i> CSF leucocyte count of $>20 \times 10^6 / \text{l}$)] [2]	G00.0-G00.9
Pneumonia	Clinical signs (fast breathing, in-drawing) <i>and</i> informed by chest x-ray <i>and</i> GBS-positive blood culture or PCR or latex agglutination [3]	P23.0-P29, J15.3

Table S1b: Impairment domain severity definitions and disability weights

Impairment (ICD10 code) [4]	Domain	Definition used in this paper (modified from GBD2013 and Nature supplement) [5, 6]	Global Burden of Disease Study 2013 (GBD2013) lay definition	GBD2013 Disability Weight
Motor (G80, G81.1, G82.1, G83.0-G83.3, G24.9, G25.3, G25.5, G25.9, F82, R26-R27)	Mild motor	Difficulty in everyday motor activities but able to move around without help.	Difficulty in moving around but is able to walk without help.	0.010 (0.005-0.019)
	Moderate motor	Difficulty in holding implements, dressing and sitting upright. Able to move around without help.	Difficulty in moving around, and difficulty in lifting and holding objects, dressing and sitting upright, but is able to walk without help.	0.061 (0.040-0.089)
	Severe motor	Inability to walk and absence of functional use of hands.	Unable to move around without help, and not able to lift or hold objects, get dressed or sit upright.	0.402 (0.268-0.545)
Intellectual (F70-F79, F80.0, F81.0, F81.2, F81.8, F81.9, F06.7)	Mild intellectual	Cognitive Z-score -1 to -2 SD for test (DQ 70-84)	Low intelligence and is slow in learning at school.	0.043 (0.026, 0.064)
	Moderate intellectual	Cognitive Z-score -2 to -3 SD for test (DQ 55-69)	Low intelligence, and is slow in learning to speak and to do even simple tasks.	0.100 (0.066, 0.142)
	Severe intellectual	Cognitive Z-score ≤ 3 for test (DQ < 55)	Very low intelligence and cannot speak more than a few words, needs constant supervision and help with most daily activities, and can do only the simplest tasks.	0.160 (0.107, 0.226)
	Profound intellectual	Cognitive Z-score ≤ 3 for test (DQ < 55)	Very low intelligence, has almost no language, and does not understand even the most basic requests or instructions. Requires constant supervision and help for all activities.	0.200 (0.133, 0.283)
Motor and intellectual	Mild motor and intellectual	Mild motor and mild intellectual	Some difficulty in moving around but is able to walk without help. Slow in learning at school.	0.031 (0.018, 0.050)

	Moderate motor and intellectual	Moderate motor and intellectual impairment	Some difficulty in moving around, holding objects, dressing and sitting upright, but can walk without help. Low intelligence and is slow in learning to speak and to do simple tasks.	0.203 (0.134, 0.290)
	Severe motor and intellectual	Severe motor and severe intellectual	Cannot move around without help, and cannot lift or hold objects, get dressed or sit upright. Very low intelligence, speaks few words, and needs constant supervision and help with all daily activities.	0.542 (0.374, 0.702)
Visual (H47, H48-H51, H53.0, H53.2, H53.4, H54.4-H54.7)	Mild visual	Visual acuity in best eye <6/12 but better or equal to 6/185 or corresponding visual field loss	Some difficulty with distance vision, for example reading signs, but no other problems with eyesight.	0.003 (0.001-0.007)
	Moderate visual	Visual acuity in best eye between 6/18 and 6/60, or corresponding visual field loss	Vision problems that make it difficult to recognize faces or objects across a room.	0.031 (0.019-0.049)
	Severe visual	Visual acuity in best eye between 6/60 and 3/60, or corresponding visual field loss	Severe vision loss, which causes difficulty in daily activities, some emotional impact (for example worry), and some difficulty going outside the home without assistance.	0.184 (0.125-0.258)
	Blind	Visual acuity in best eye <3/60, or corresponding visual field loss	Completely blind, which causes great difficulty in some daily activities, worry and anxiety, and great difficulty going outside the home without assistance.	0.187 (0.124-0.260)
Hearing (H90.3-H90.7)	Mild hearing	Audiometric hearing threshold level 26-30 decibel	Great difficulty hearing and understanding another person talking in a noisy place (for example, on an urban street).	0.010 (0.004, 0.019)
	Moderate hearing	Audiometric hearing threshold level 31-64.9 decibel	Unable to hear and understand another person talking in a noisy place (for example, on an urban street), and has difficulty hearing another person talking even in a quiet place or on the phone.	0.027 (0.015, 0.042)
	Severe hearing	Audiometric hearing threshold level 65-89.9 decibel	Unable to hear and understand another person talking, even in a quiet place, and unable to take	0.158 (0.105, 0.227)

		part in a phone conversation. Difficulties with communicating and relating to others cause emotional impact at times (for example worry or depression).	
Profound hearing	Audiometric hearing threshold level >90 decibel	Unable to hear and understand another person talking, even in a quiet place, is unable to take part in a phone conversation, and has great difficulty hearing anything in any other situation. Difficulties with communicating and relating to others often cause worry, depression or loneliness.	0.204 (0.134, 0.288)
Complete hearing loss	Cannot hear at all in any situation including even the loudest sounds	Cannot hear at all in any situation, including even the loudest sounds, and cannot communicate verbally or use a phone. Difficulties with communicating and relating to others often cause worry, depression or loneliness.	0.215 (0.144, 0.307)

Table S2: World Health Organization International Classification of Functioning, Disability and Health definitions [7]

Term	Definition
Impairment	problems in body function and structure such as significant deviation or loss
Activity limitation	a difficulty encountered by an individual in executing a task or action
Participation restriction	a problem experienced by an individual in involvement in life situations
Disability	an umbrella term, covering impairment, activity limitation, and participation restriction

Table S3: Search terms

Brain Damage, Chronic [MeSH Terms]	Epilepsy	sequel*
Cerebral palsy [MeSH Terms]	Seizures [MeSH Terms]	outcome
Cerebral palsy	Seizures	Development
Cerebral AND palsy	Vision Disorders [MeSH Terms]	Neurodevelopment*
Disabled Children [MeSH Terms]	Blindness	Neuro-development*
Mental Disorders Diagnosed in Childhood [MeSH Terms]	Blind	Death
Mental Retardation [MeSH Terms]	Hearing Loss, Sensorineural [MeSH Terms]	Mortality
Learning Disorders [MeSH Terms]	Hearing Loss, Sensorineural [MeSH Terms]	Case AND Fatality AND rate
Communication Disorders [MeSH Terms]	Hearing Loss	Fatality
Developmental Disabilities [MeSH Terms]	Hearing AND loss	Death [MeSH Terms]
Cognitive AND impairment	Deafness [MeSH Terms]	Mortality [MeSH Terms]
Motor AND impairment	Prognosis [MeSH Terms]	Morbidity [MeSH Terms]
Epilepsy [MeSH Terms]	Impairment	Case fatality rate [MeSH Terms]

AND

Streptococcus
 Streptococcal
 Streptococci AND (Group AND B) or Agalactiae
 Streptococcus Agalactiae [MeSH Terms]

Table S4: Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Population	Invasive GBS disease Index case <90 days of life	Non-representative sample (e.g. all preterm infants, all stroke survivors)
Case definition	Neurodevelopmental outcomes reported at ≥ 6 months	Cases not pathogen-specific
Laboratory	GBS confirmed by blood / CSF culture or PCR or latex agglutination	
Search	No language or date restrictions	
Article type		Review articles, case reports

Table S5: Neurodevelopmental impairment in survivors of infant Group B *Streptococcus* sepsis

UN region	UN sub-region	Country	Author	Publication year	Median year data collection	NMR (per 1000 live births)	No. of GBS sepsis survivors	No. of GBS sepsis survivors with any NDI (%)	No. of GBS sepsis survivors with mod-sev NDI (%)
Africa	Southern Africa	South Africa	Dangor	(unpublished)	2014	11	70	13 (18.6)	5 (7.1)
		USA	Horn	1974	unknown	12	4	0 (0)	0 (0)
Europe	Northern Europe	UK	Heath	(unpublished)	2015.5	2	61	5 (8.2)	1 (1.6)
		Denmark	Carstensen	1985	1980.5	6	36	1 (2.8)	0 (0)
	Western Europe	Germany	Schroder	1982	1975.5	9	8	2 (25)	1 (12.5)

NDI=Neurodevelopmental impairment, NMR=neonatal mortality rate, mod-sev=moderate to severe

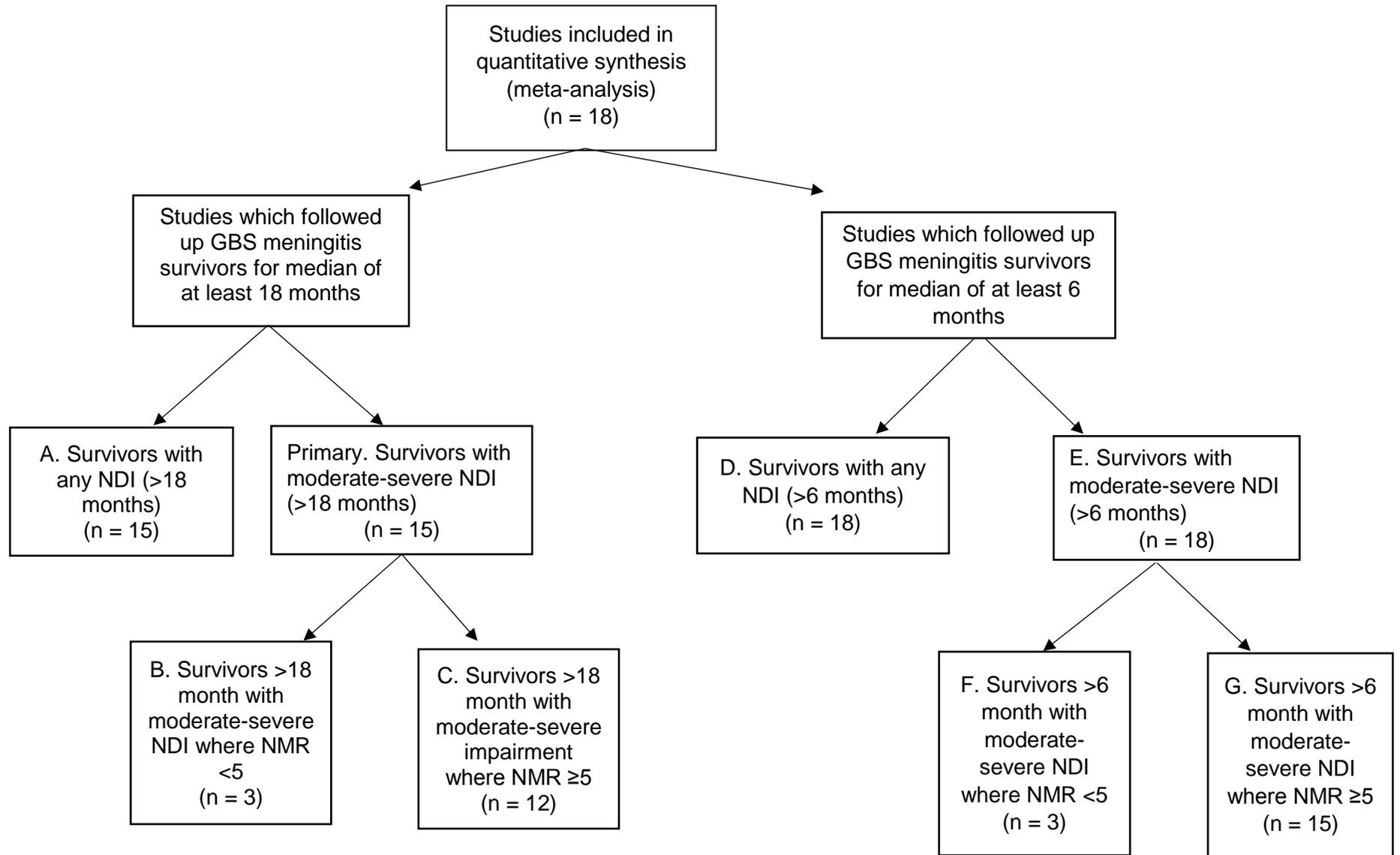
Table S6: Neurodevelopment Assessments

UN Region	Author	No. of assessments	Age(s) of child at time of assessment (years)	Cognitive	Motor	Language	Vision	Hearing	Socio-emotional / Behavioural
Africa	Dangor	3	0.3, 0.5, 1.0	-	DDST II, Paed. exam	DDST II, Paed. exam	-	-	DDST II
	Ben Hamouda	1	Range: 1.0-9.0	Paed. exam	Paed. exam	Paed. exam	VER	BAER	Paed. exam
Americas	Libster	1	Range: 3.0-12.0	WIAT II	MSEL, CDI Paed. Exam	MSEL, CDI	MSEL, SVAC	Audiometry	PEDS, CDI
	Franco	19	0.3, 0.5, 0.8, 1, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 11.0, 12.0, 13.0, 14.0	SBIS, CIIS WISC, WPPSI	Paed. Exam	(Method not described)	(Method not described)	(Method not described)	-
	Wald	1	Range: 3.0-18.0	WPPSI, WISC, MSCA, WRAT, SAT	GPT, BVMI	-	BVMI	Audiometry	CBC, VABS
	Chin	5	0.5, 0.8, 1.0, 1.5 then Range: 5.0-7.0	BSID, WPPSI, WISC	BSID, Paed. exam	BSID	Fundoscopy, refraction	SFA	-
	Edwards	1	Range: 3.3-9.0	BSID, MCDI, WJPEB	BSID, MCDI	BSID, PLS, PPVT, EOPT, CELI, ITPA, TELD	Ophthalm. exam	ENT exam	Psych. exam
	Haslam	1	Range: 0.6-6.9	BSID, SBIS, WISC, psych. exam	BSID, Paed. exam	BSID	(Method not described)	PTA, BOA	Psych. exam
	Horn	1	Range: 1.1-3.5	-	DDST II, Paed. Exam	DDST II, Paed. exam	-	-	DDST II
	Baker	1	Range: 0.5-2.0	Q'aire to paed.	Q'aire to paed.	-	-	-	-
	Asia	Wee	4	0.5, 1.0, 2.0, 5.0	Paed. exam	Paed. Exam	Paed. Exam	(Method not described)	ENT exam
Zhu		1	Range: 0.8-2.0	-	Q'aire to	-	-	-	-

					parents				
Europe	Bedford	1	5.0	Q'aire to parents	Q'aire to parents	Q'aire to parents	Q'aire to parents	Q'aire to parents	Q'aire to parents
	Bennhagen	1	Range: 1.3-2.3	GP/paed. exam	GP/paed. Exam	GP/paed. exam	(Method not described)	(Method not described)	-
	Carstensen	Not reported	Range :0.3-5.0	Paed. exam	Paed. Exam	Paed. Exam	(Method not described)	(Method not described)	-
	Heath	1	Range: 2.0-4.0	BSID	BSID	BSID	Health assessment	Health assessment	-
	Schroder	1	Range: 0.8-13.0	-	DDST II	MFDD, DDST II	(Method not described)	Audiometry	DDST II

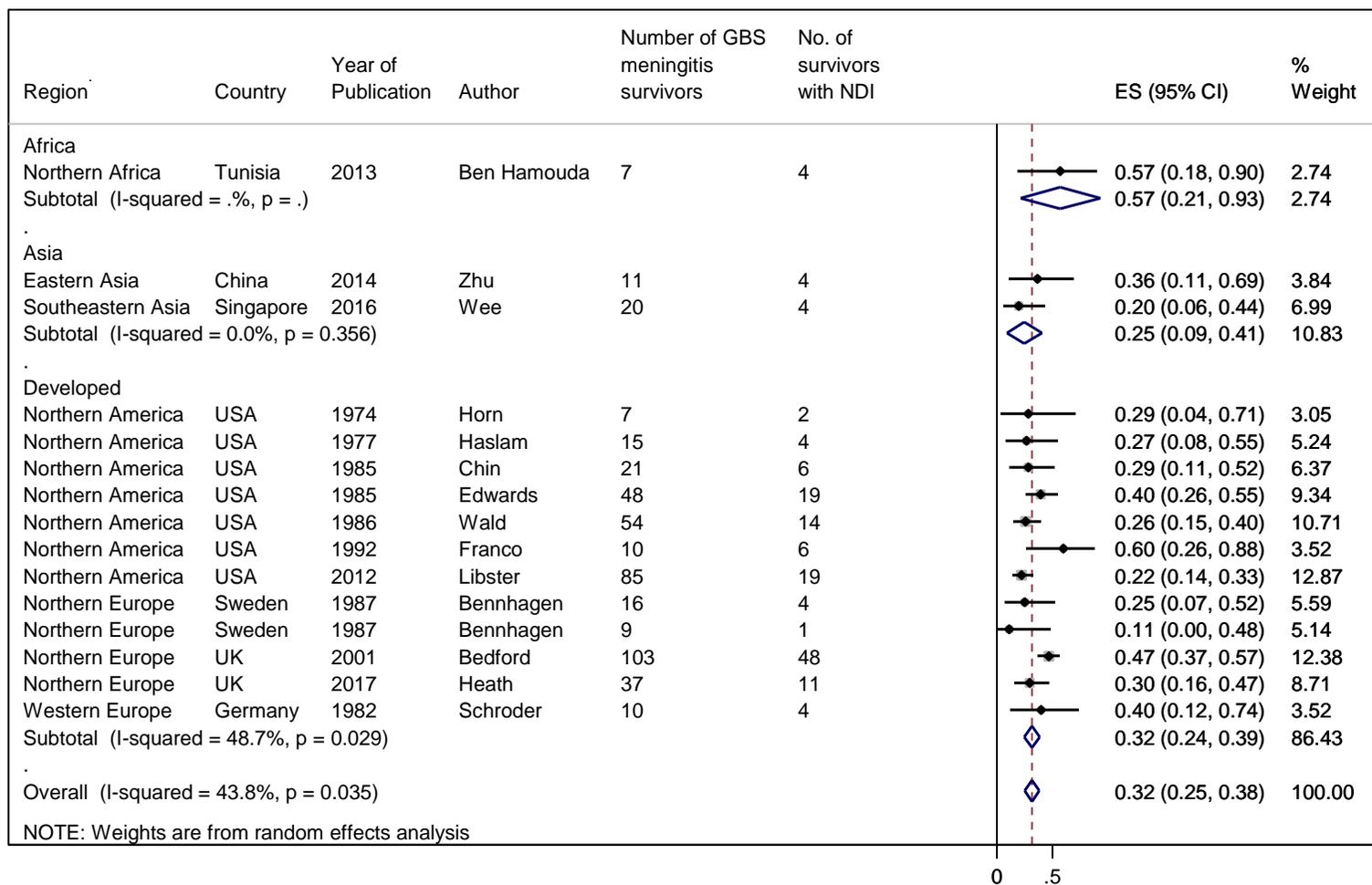
BA ER – Brainstem auditory evoked response, BVMI – Beery Test of Visual-Motor Integration [8], BOA – Behavioural Observation Audiometry [9], BSID – Bayley’s Scales of Infant Development [10], CBC – Child Behaviour Checklist [11], CDI – Child Development Inventory [12], CELF - Carrow Elicited Language Inventory [13], CIIS – Cattell Infant Intelligence Scale [14], DDST II – Denver Developmental Screening Test II [15], ENT exam – otolaryngologist examination, EOWPT - Expressive One Word Picture Vocabulary Test [16], GP exam - Neurological / developmental examination by General Practitioner, GPT - Grooved Pegboard Test [17], ITPA - Illinois Test of Psycholinguistic Abilities [18], MCDI - Minnesota Child Development Inventory [19], MFDD - Munich Functional Development Diagnostic [20], MSCA - McCarthy Scale of Children’s Abilities [21], MSEL - Mullen’s Scale of Early Learning [22] , Ophthalm. Exam – ophthalmologist examination, Paed. Exam – Neurological / developmental examination by paediatrician, PEDS – Parent Evaluation of Development Status [23], PLS – Preschool Language Scale [24], PPVT - Peabody Picture Vocabulary Test [25], PTA – Pure Tone Audiometry [26], Psych. Exam – psychologist examination, Q’aire – Questionnaire, SAT – school achievement test, SBIS – Stanford-Binet Intelligence Scales [27], SFA – Sound Field Audiometry [28], SVAC - Snellen Visual Acuity Chart [29], TELD - Test of Early Language Development [30], VABS – Vineland Adaptive Behaviour Scales [31], VER – Visual Evoked Response, WIAT II – Weschler Individual Achievement Test II [32], WISC – Weschler Intelligence Scale for Children [33], WJPEB - Woodcock-Johnson Psycho-Educational Battery [34], WPPSI – Weschler Preschool and Primary Scale [35], WRAT – Wide Range Achievement Test [36]

Figure S1: Organogram of meta-analyses performed with number of studies included in each meta-analysis



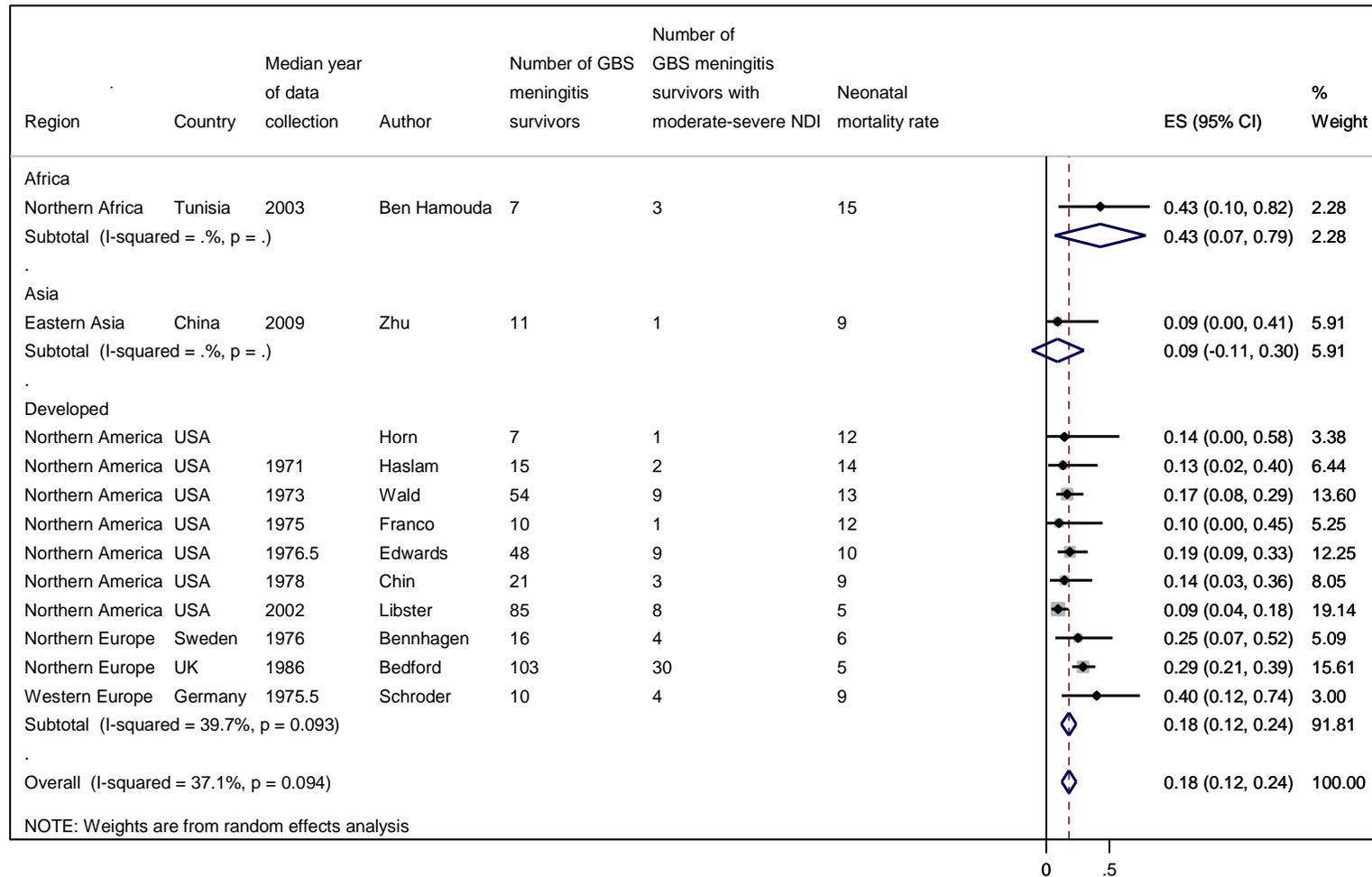
NDI=Neurodevelopmental impairment, NMR=neonatal mortality rate (per 1000 live births)

Figure S2: Meta-analysis A. Infant Group B *Streptococcus meningitis* survivors followed up for median of ≥ 18 months with any NDI



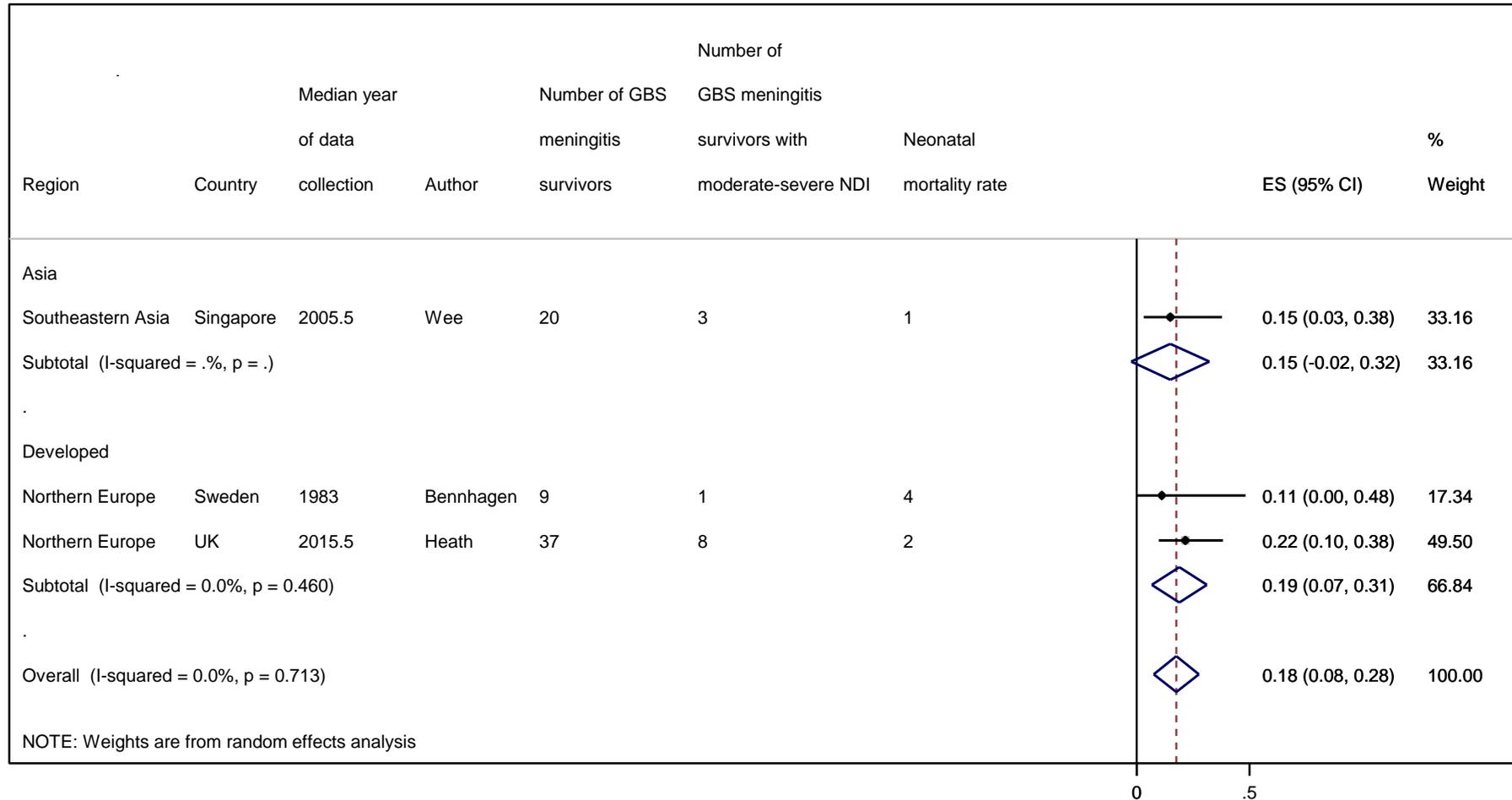
ES=Effect size, NDI=Neurodevelopmental impairment

Figure S3: Meta-analysis B. Infant Group B *Streptococcus meningitis* survivors followed up for median of ≥ 18 months with moderate-severe NDI where $NMR \geq 5 / 1000$



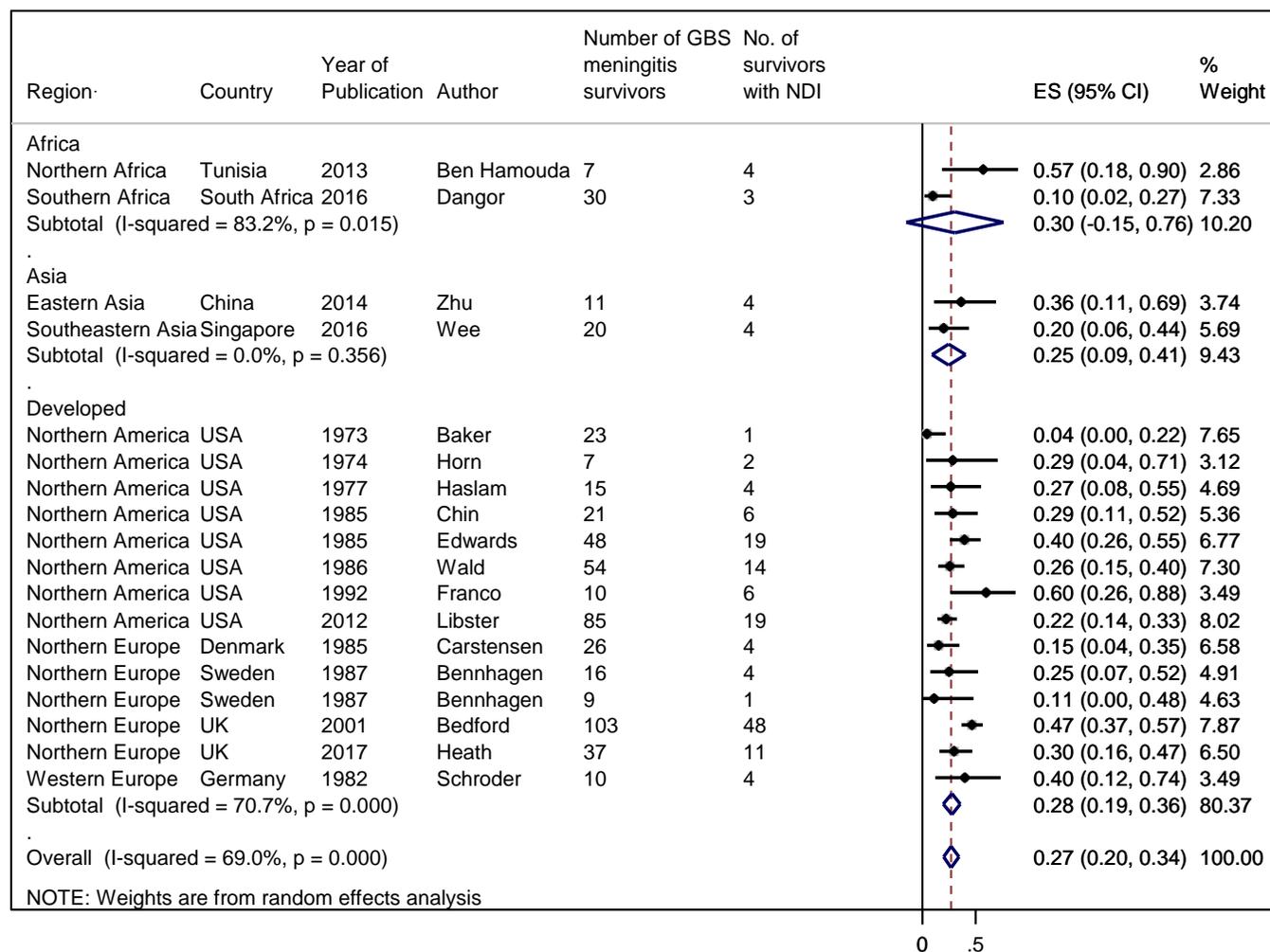
Note: Where median year of data collection unknown (Horn, 1974) [37], neonatal mortality rate at year of publication used.
ES=Effect size, NDI=Neurodevelopmental impairment

Figure S4: Meta-analysis C. Infant Group B *Streptococcus meningitis* survivors followed up for median of ≥ 18 months with moderate-severe NDI where neonatal mortality rate (NMR) $< 5 / 1000$



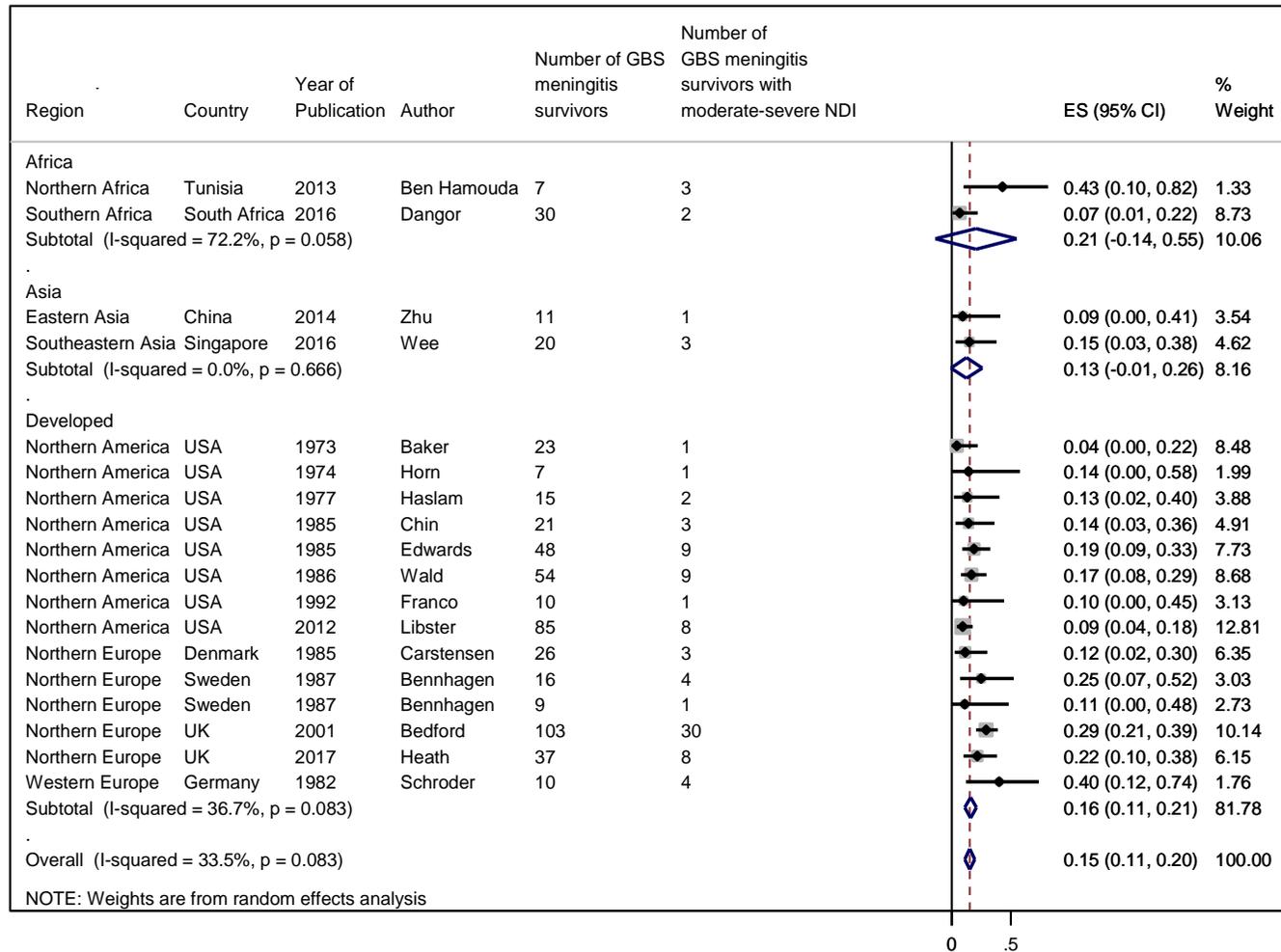
ES=Effect size, NDI=Neurodevelopmental impairment

Figure S5: Meta-analysis D. Infant Group B *Streptococcus meningitis* survivors followed up for median of ≥ 6 months with any NDI



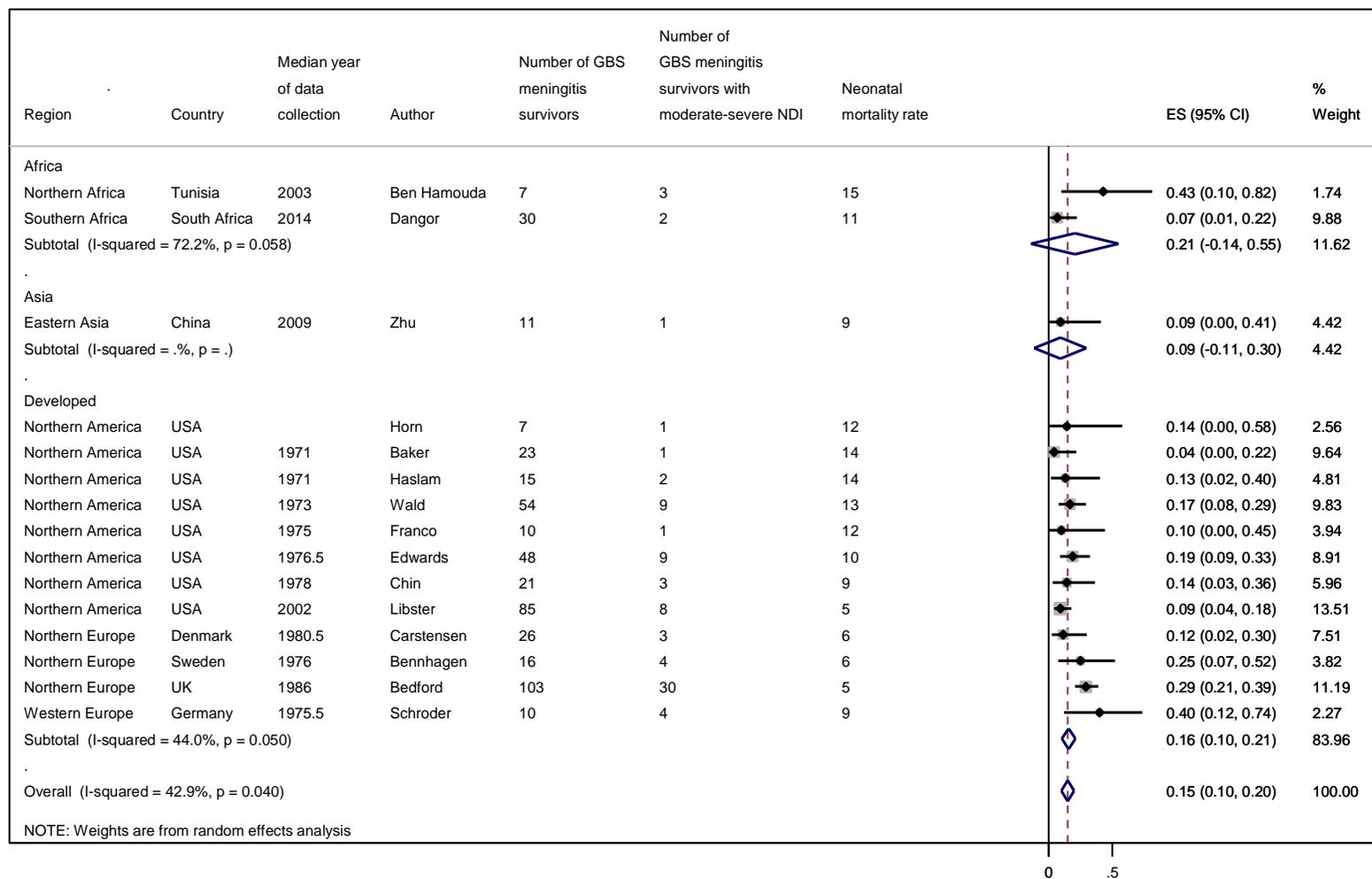
Note: Where study has not yet been published, 'Year of Publication' refers to final year of data collection
 ES=Effect size, NDI=Neurodevelopmental impairment

Figure S6: Meta-analysis E. Infant Group B *Streptococcus meningitis* survivors followed up for median of ≥6 months with moderate-severe NDI



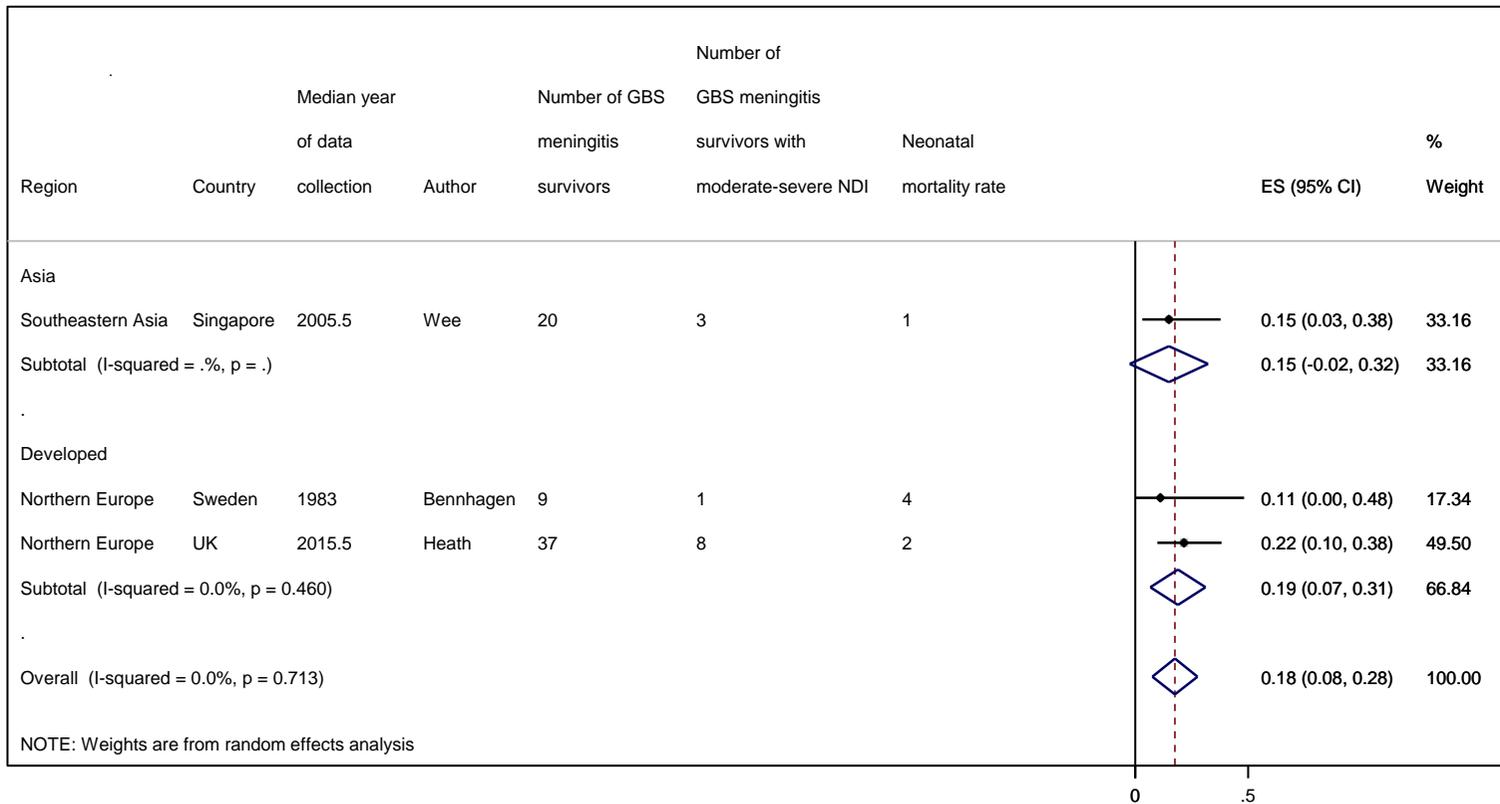
Note: Where study has not yet been published, 'Year of Publication' refers to final year of data collection
 ES=Effect size, NDI=Neurodevelopmental impairment

Figure S7: Meta-analysis F. Infant Group B *Streptococcus meningitis* survivors followed up for median of ≥ 6 months with moderate-severe NDI where $NMR \geq 5 / 1000$



Note: Where median year of data collection unknown (Horn, 1974) [37], neonatal mortality rate at year of publication used. ES=Effect size, NDI=Neurodevelopmental impairment

Figure S8: Meta-analysis G. Infant Group B *Streptococcus meningitis* survivors Group B *Streptococcus meningitis* survivors followed up for median of ≥ 6 months with moderate-severe NDI where NMR $< 5 / 1000$



ES=Effect size, NDI=Neurodevelopmental impairment

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