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Supplement to Biomarkers in Body Fluids as Indicators of Skeletal Maturity: A Systematic Review and Meta-analysis

Kapoor P, Balachandran R, Chowdhry A, Perinetti G, Kharbanda OP. Biomarkers in Body Fluids as Indicators of Skeletal Maturity: A Systematic Review and Meta-analysis. *Rambam Maimonides Med J* 2023;September 1. Review. doi:10.5041/RMMJ.10506 [Epub ahead of print].

Supplementary Table 1. Search Strategy Applied in Different Databases.

Database	Search Strategy
PubMed	(puberty OR pubertal OR skeletal maturation OR skeletal maturity OR skeletal development OR bone age OR skeletal age OR facial growth OR mandibular growth OR maxillary growth OR growth phase OR growth peak OR spurt OR height peak) AND (molecule OR molecules OR enzyme OR enzymes OR factor OR factors OR marker OR markers OR biomarker OR biomarkers OR hormone OR hormones) AND (GCF OR crevicular OR saliva OR salivary OR serum OR blood) AND (cervical vertebral maturation OR cervical stage OR cervical maturation OR CVMI OR CVM OR MP3 OR third finger middle phalanx OR MPM OR Fishman OR Greulich Pyle OR Greulich-Pyle OR Lamparski OR Hassel Farman OR hand wrist OR hand-and-wrist OR standing height)
Scopus	((("skeletal maturation" OR "skeletal age" AND (gcf OR crevicular OR saliva OR salivary OR serum OR blood) AND (orthodontics) AND (biomarkers))
Web of Science	TS=((puberty OR pubertal OR "skeletal maturation" OR "skeletal maturity" OR "skeletal development" OR "bone age" OR "skeletal age" OR "facial growth" OR "mandibular growth" OR "maxillary growth" OR "growth phase" OR "growth peak" OR spurt OR "height peak") AND (molecule OR molecules OR enzyme OR enzymes OR factor OR factors OR marker OR markers OR biomarker OR biomarkers OR hormone OR hormones) AND (GCF OR crevicular OR saliva OR salivary OR serum OR blood) AND ("cervical vertebral maturation" OR "cervical stage" OR "cervical maturation" OR CVMI OR CVM OR MP3 OR "third finger middle phalanx" OR MPM OR Fishman OR Greulich Pyle OR Greulich-Pyle OR Lamparski OR Hassel-Farman OR hand wrist OR hand-and-wrist OR "standing height"))

Database	Search Strategy
Embase	('puberty'/exp OR puberty OR pubertal OR 'skeletal maturation'/exp OR 'skeletal maturation' OR 'skeletal maturity'/exp OR 'skeletal maturity' OR 'skeletal development'/exp OR 'skeletal development' OR 'bone age'/exp OR 'bone age' OR 'skeletal age'/exp OR 'skeletal age' OR 'facial growth'/exp OR 'facial growth' OR 'mandibular growth' OR 'maxillary growth'/exp OR 'maxillary growth' OR 'growth phase'/exp OR 'growth phase' OR 'growth peak' OR spurt OR 'height peak') AND ('molecule'/exp OR molecule OR 'molecules'/exp OR molecules OR 'enzyme'/exp OR enzyme OR 'enzymes'/exp OR enzymes OR factor OR factors OR 'marker'/exp OR marker OR markers OR 'biomarker'/exp OR biomarker OR 'biomarkers'/exp OR biomarkers OR 'hormone'/exp OR hormone OR 'hormones'/exp OR hormones) AND (gcf OR crevicular OR 'saliva'/exp OR saliva OR salivary OR 'serum'/exp OR serum OR 'blood'/exp OR blood) AND (((('cervical vertebral maturation' OR 'cervical stage' OR 'cervical maturation' OR cvmi OR cvm OR mp3 OR 'third finger middle phalanx' OR mpm OR fishman OR greulich) AND pyle OR 'greulichpyle' OR lamparski OR 'hasselfarman' OR 'hand'/exp OR hand) AND ('wrist'/exp OR wrist) OR 'hand and wrist' OR 'standing height'/exp OR 'standing height')
Directory of Open Access Journals (DOAJ)	biomarkers AND orthodontics AND skeletal maturation

See next pages for Supplemental Table 2, and Supplemental Figures 1 and 2.

Supplementary Table 2. Inclusion and Exclusion Criteria for Studies.

Inclusion Criteria	Exclusion Criteria
All original studies on humans including clinical trials, prospective or retrospective cohort studies, studies mentioning on both biomarkers and skeletal maturation, studies that compare biomarkers with radiographic assessment of skeletal maturation	In-vitro studies, animal studies, studies on biomarkers but not on skeletal maturation, studies on skeletal maturation but not on biomarkers, studies with no radiographic comparator, studies in unhealthy patients or those undergoing treatment, case reports, and reviews/opinions

See next pages for Supplemental Figures 1 and 2.

Study	Risk of Bias Domains				
	D1	D2	D3	D4	Overall
Alhazm 2019	+	+	+	+	+
Tripathi T 2017	+	+	+	+	+
Tripathi T 2019	+	+	+	+	+
Tripathi T 2018	+	+	+	+	+
Jain N 2017	+	+	+	+	+
Hegde SS 2018	+	×	×	+	×
Sinha M 2016	+	+	+	+	+
Wen Xi 2018	+	+	+	+	+
Gupta S 2012	+	+	+	+	+
Hussain MZ 2013	+	+	+	+	+
Anusuya V 2020	+	+	+	+	+
Masoud M 2008	+	+	+	+	+
Ishaq 2008	+	+	+	+	+
Gupta S 2015	+	+	+	+	+
Nayak S 2014	+	+	+	+	+
Perinetti G 2012	+	+	+	+	+
Perineeti G 2011	+	+	+	+	+
Masoud M 2015	+	+	+	+	+
Masoud M 2009	+	+	+	+	+
Srinivasan B 2012	+	+	+	+	+
Jain S 2013	+	+	+	+	+
Maosud M 2012	+	+	+	+	+
Wen Xi 2021	+	-	-	+	-
Wijaya H 2019	+	+	+	+	+
Wen Xi 2016	+	+	+	+	+
Masoud 2015	+	+	+	+	+
Venkatgiriappa S 2016	+	+	+	+	+
Soumya J 2016	+	+	-	+	-
Wijay H 2018	+	+	-	+	-
Nancy ED 2019	+	-	-	+	-
Perineeti G 2016	+	+	+	+	+
Irham 2018	+	+	-	-	-
Tarvade 2015	×	×	+	+	×
Meshari 2022	+	+	+	+	+
Sookhakian 2022	+	+	+	+	+
Carelli 2021	+	+	+	+	+
Trehan 2021	+	+	-	+	-
Almalki, 2022a	+	+	+	+	+
Almalki 2022b	+	+	+	+	+
Tsagkari 2022	+	+	+	+	+
Kahlon 2021	+	+	+	+	+

Legend**Domains**

D1: Patient selection

D2: Index test

D3: Reference standard

D4: Flow and timing

Judgment

High



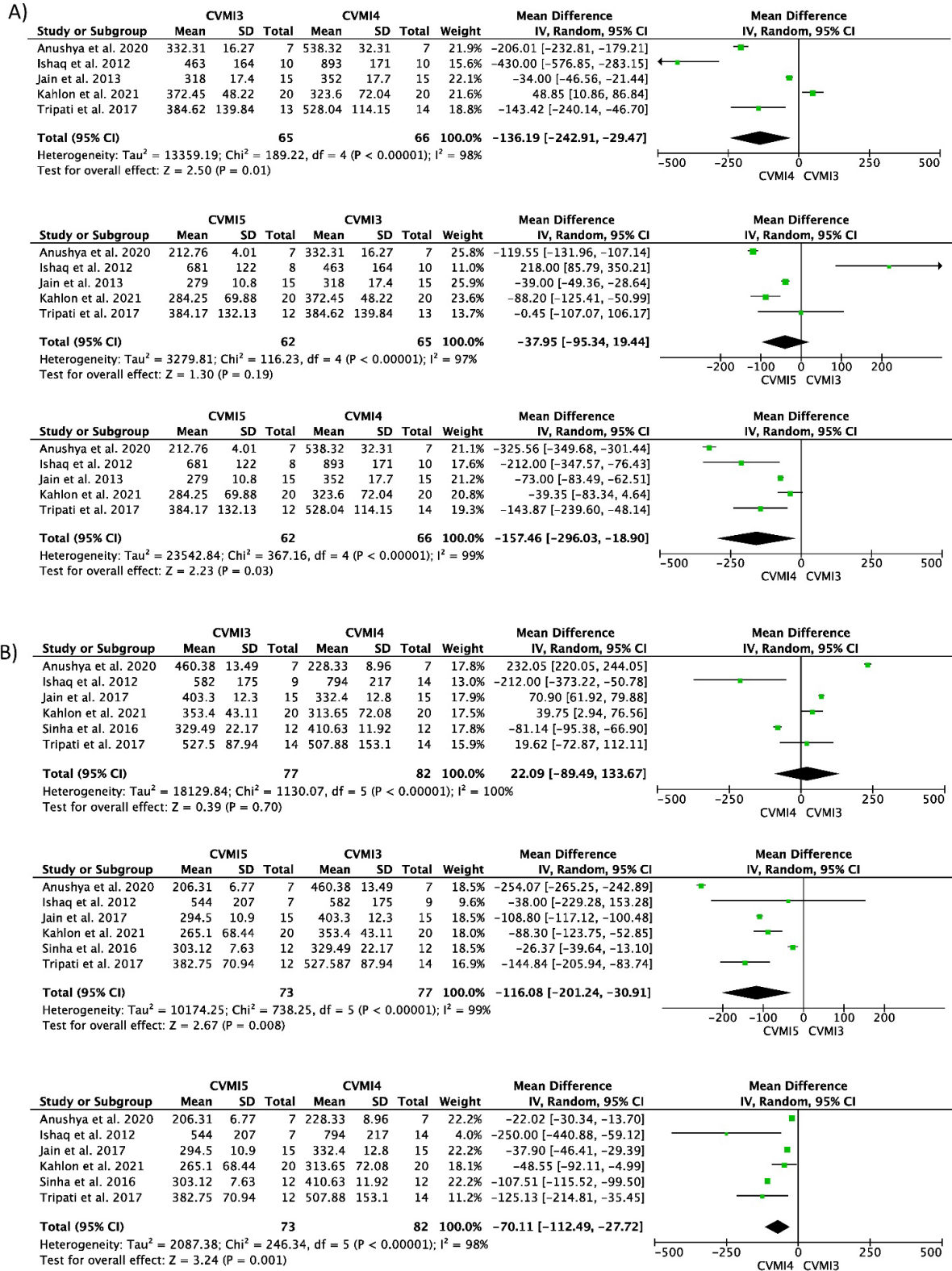
Some concerns



Low

Supplementary Figure 1. Quality Assessment by QUADAS-2 Tool.

Quality assessment of 41 total eligible studies, and exclusion of 6 studies on the basis of an unclear risk of bias; high risk of bias in two studies.



Supplementary Figure 2. Comparison of Serum IGF-1 Levels Between CVM 3, 4, 5 in Males (A) and Females (B).
The CVM staging is also referred to as cervical stages (CS).

CVM, cervical vertebral maturation index.